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IMMUNO-SEROLOGIC STUDIES OF THE IMMEDIATE WHEAL-TYPE ALLERGIES

A PRELIMINARY REPORT

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DURING the past year we have continued our studies to determine, if possible, the location of the skin sensitizing antibody in certain fractions of ragweed-reacting sera. Newell[1] has shown that this antibody was present in the electrophoretically separated gamma globulin. Campbell and associates[2] have reported skin-sensitizing activity in other serum fractions. In the studies[3] we reported last year the indications were that the antibody could not be accounted for in its entirety in the gamma globulin fraction and our further studies confirm this view.

Generally, the isolation of individual electrophoretic main components from sera can be applied only to the fact and slow moving end components, namely, albumin and gamma globulin. Mixtures of end components as albumin and alpha$_1$ globulin or gamma and beta globulin may be obtained in bulk if electrophoretic separation is carried out in macro scale. Such mixtures may then be further separated by subsequent re-electrophoresis. In the study of some sera we have combined chemical fractionation with electrophoretic separation and analysis in order to obtain further data.

In our current work we have preferred to express the end point of reactivities, as obtained by passive transfer test, not in terms of dilution but rather in terms of the actual amount of the protein component injected into the skin site. These amounts were calculated on the basis of colorimetric or refractometric evaluations of the sera and their fractions. From these data and the electrophoretic analysis the amount of each component present in each site was then calculated. Details of experimental procedures will be given in a future report.

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TABLE I. ELECTROPHORETIC AND IMMUNOLOGICAL DATA ON RBR. SERUM AND CERTAIN DERIVED FRACTIONS

	PER CENT COMPOSITION*					MICROGRAMS INJECTED AT END-POINT REACTIVITY						REACTION AT END-POINT	PER CENT OF REACTION DUE TO GAMMA GLOBULIN
	ALBUMIN	$ALPHA_1$	$ALPHA_2$	BETA	GAMMA	TOTAL PROTEIN	ALBUMIN	$ALPHA_1$	$ALPHA_2$	BETA	GAMMA		
A Serum	52.2	7.0	10.7	15.4	14.7	9.55	5.0	0.7	1.0	1.5	1.4	+	13
B Fr. I	86.7	9.8	3.5	0	0	1535	1331	150	54	0	0	-	
	+++						265					-	
C Fr. I-F													
D Fr. I-S		+?	+++						90			-	
E Fr. III	0	0	9.1	21.1	69.8	9.0	0	0	0.8	1.9	6.3	+	57
F Fr. III-F	0	0	+++	+?			0	0		90		-	
G Fr. III-S					+++						11	+	100
Column	1	2	3	4	5	6	7	8	9	10	11	12	13

*Fraction distribution in relative concentrations where electrophoretic analyses performed. Qualitative estimates expressed for other fractions as follows: necessarily present: +++; likely, though not necessarily present: +?. Fractions I and III (B and E, respectively) represent the ascending and descending endcomponents obtained from Rbr. serum on electrophoresis in macro scale in phosphate buffer pH 7.8, ionic strength 0.1. Fr. I-F (C) is the separated ascending, Fr. I-S (D) is the separated descending endcomponent of Fr. I, obtained on re-electrophoresis in barbiturate buffer. Likewise Fr. III-F (F) and Fr. III-S (G) are the separated ascending and descending endcomponents obtained on re-electrophoresis of Fr. III in barbiturate buffer. According to the method of preparation Fr. I-F and Fr. III-S can be considered as highly pure albumin and gamma globulin, respectively.

Sites were prepared by the injection of 0.1 ml. of ragweed-reacting serum or its fraction. The sites were tested in the usual manner. Pertinent data as obtained with one of several sera studied (Rbr) are summarized in Table I.

ALBUMIN AND ALPHA$_1$ GLOBULIN

First let us consider the question of the albumin and alpha$_1$ globulin fractions. In the total serum, passive transfer tests yielded an end-point reaction with the Rbr. serum in a skin site containing 5 micrograms of albumin (A, column 7). In the electrophoretically separated fraction I a site containing 1,331 micrograms albumin (B, column 7) yielded no reaction and with Fr. I-F in a site containing 265 micrograms of albumin (C, column 7) there was also no reaction; thus it seems proper to conclude that albumin as such does not carry any skin-sensitizing antibody. In both of these tests, let it be noted, detectable beta and gamma globulin were absent.

Now as to the alpha$_1$ globulin; an end-point reaction was obtained with the total serum when alpha$_1$ was present in the amount of 0.7 microgram in the test site (A, column 8). However, in a test with fraction I, when 150 micrograms of alpha$_1$ were present in the skin site, there was no reaction (B, column 8); hence it would seem that alpha$_1$ does not contain skin-sensitizing antibody.

GAMMA GLOBULIN

Let us now consider the question of the gamma globulin fraction and its immunologic property of skin sensitization. In the original unseparated serum, a positive end-point reaction was obtained in a skin site containing 1.4 micrograms of gamma globulin (A, column 11). Referring now to fraction III which contained in addition to the predominant gamma globulin also beta and alpha$_2$ globulin, an end-point reaction was obtained in the site containing 6.3 micrograms of gamma globulin (E, column 11) and in fraction III-S the end-point reaction was obtained in the site which contained 11 micrograms of gamma globulin (G, column 11). Since it appears that 11 micrograms of gamma globulin alone account for the endpoint reaction in fraction III-S, one may calculate that the 1.4 micrograms of the gamma globulin in the original serum account only for 13 per cent of the reactivity of the serum. One must of course understand that all protein components included in the gamma globulin do not necessarily contain sensitizing antibody, but also in many other experiments that we have done, reactive gamma globulin has been separated from most of the sera but has accounted for only from 13 per cent to 25 per cent of the total serum reactivity, never 100 per cent; however, there have been serum fractions in which no detectable gamma globulin was present and reactivity was nevertheless obtained. In other words, gamma globulin is not essential for the transfer of sensitizing antibody and further there have been two instances in which purified gamma globulin did not transfer any sensitization, although the serum from which it was derived was reactive.

ALPHA$_2$ AND BETA GLOBULIN COMPONENTS

Tests with the whole serum yielded an end-point passive transfer reaction in the site containing 1.5 micrograms of beta globulin (A, column 10) and one

TABLE II. THE INDIVIDUALITY OF THE REACTIONS OF SERA FROM TYPICAL RAGWEED HAY FEVER PATIENTS

PASSIVE TRANSFER SITES*		REACTIONS OF SITES TESTED WITH THE FOLLOWING EXTRACTS†							
SERUM	MIXED WITH	LOW RAGWEED	AMARANTH	CHENOPOD	COCKLEBUR	IVA	MUGWORT	SAGE	RUSSIAN THISTLE
Hre.	Saline	++++	++	++	+ ++	++++	+++		++
Hre.	L.R. 1000 U.	0	0	0	0	0	0		0
Aar.	Saline	++	++	+++	+++	+++	++		++
Aar.	L.R. 1000 U.	0	+	+++	+	+	+		+
Wilk.	Saline	+++	++	++	++	++	+++	+++	
Wilk.	L.R. 1000 U.	++	0	0	±	+	++	++	
Elaz.	Saline	++++	+	±	+	+++	0	0	
Elaz.	L.R. 1000 U.	0	0	0	0	0	0	0	

*The various sera, Hre., Aar., etc., were mixed in equal parts with saline or low ragweed (1000 protein nitrogen units per c.c.), and 1/10 c.c. of each such mixture was injected into the skin of normal test subjects to create sites for later testing.

†Forty-eight hours after sites were made, they were tested by the injection of 1/40 c.c. of each of the various extracts into various sites as shown.

Note: If one compares both the passive transfer test (serum and saline) and the neutralization test (serum and ragweed), it will be observed that no two of these sample sera behave exactly alike.
(Reprinted from Cooke, R. A.: J. ALLERGY 15: 212, 1944.)

microgram of alpha$_2$ globulin (A, column 9); since only 13 per cent of the total reactivity is accounted for in the gamma globulin it may be reasoned that the balance of reactivity lies in the alpha$_2$ or in beta globulin or both. We have at the present time no positive direct evidence in this respect, since these components have not been separated in purified form, but there is indirect evidence that the alpha$_2$ globulin has not contributed to the reactivity of this Rbr. serum since with fraction I in a site containing 54 micrograms of alpha$_2$ globulin no reaction was obtained (B, column 9). Observations on other sera, however, do not rule out entirely a possible presence of reactivity in alpha$_2$ globulin of certain sera.

In the many samples of separated components that we have tested, beta globulin has been present in most of those that showed passive transfer capacity but we did have instances of reactivity in the entire absence of detectable beta or alpha$_2$ globulin.

As yet, we have not been able to account for the totality of serum reactivity in any instance, where sera were likewise fractionated electrophoretically and where the reactivities of the isolated fractions were evaluated quantitatively in the manner outlined. As the results so far obtained do not permit a general unqualified interpretation, we shall continue our studies on this point. On the other hand, about 75 per cent of the activity of a sensitizing plasma was accounted for by the reactivities of the plasma fractions obtained according to Cohn's Method 10.[5, 6*] Continued electrophoretic-chemical studies using this method are in progress.

In reviewing the sum total of our studies, one significant fact seems to emerge and that is the variation that has been found in sera from different ragweed-sensitive patients as to the location of the sensitizing antibody in the alpha$_2$, beta and gamma globulin fractions. This is in conformity with the previous biological studies which indicate what was described as a "finger-print individuality" of the ragweed sensitizing sera,[4] since the antibodies of such sera when studied in detail with regard to their reactivities and neutralizations show definite though sometimes minor biologic variations (Table II).

SUMMARY

1. The skin-sensitizing antibody for ragweed has not thus far been found to exist in the albumin or alpha$_1$ components of serum. It appears to exist in gamma globulin, but with variations.

2. It appears to exist in the beta and possibly in the alpha$_2$ globulin or in the interzones to these components.

3. Neither gamma globulin nor beta globulin nor alpha$_2$ is essential to skin reactivity since reactions have been found in the absence of each of these components in electrophoretically detectable amounts.

4. The differences observed in different sera suggest a variation in the distribution of the sensitizing antibody through the globulin area and in this way agrees with the biological variations that ragweed sensitive sera have been shown to possess.

*These latter experiments were carried out jointly with Miss Ella M. Russ, B.S., of the Department of Medicine of the New York Hospital-Cornell Medical Center, New York.

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PARTITION OF THE SKIN-SENSITIZING ANTIBODY AMONG ALCOHOL-FRACTIONATED PLASMA PROTEINS

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IN PREVIOUS studies allergic (skin-sensitizing) antibodies[1] have been reported to be among the gamma globulins of serum proteins separated by classical electrophoretic techniques. Recently, however, Campbell and associates,[2] have reported the concentration of these antibodies in the alpha and beta globulin component of serum proteins separated by the newer electrophoretic-convection procedure. The present paper describes our studies on the reagin content of the plasma proteins of four patients with ragweed hay fever fractionated by Cohn's alcohol precipitation method.[3]

METHODS

Plasma Fractionations.—Ten ml. of fasting venous blood was obtained by venepuncture and immediately mixed with 1.75 ml. of a solution of 2.2 Gm. per cent dextrose, 2.2 Gm. per cent sodium citrate, and 0.8 Gm. per cent citric acid. The blood was centrifuged at 2,000 r.p.m. for 15 to 20 min. to obtain a clear plasma. Five ml. of this plasma was then fractionated by Cohn's alcohol precipitation technique (Method 10) as modified by Lever and associates.[4] Fractions I, II, and III were precipitated at –5° C. in an ethanol concentration of 19 per cent, pH 5.8 to 5.9, and ionic strength of 0.04 M. The supernatant and washing of this precipitate were combined and Fraction IV+V precipitated in 0.01 M. zinc acetate. The I+II + III precipitate was twice extracted for Fraction II with a 14 per cent alcoholic solution at pH 5.5, ionic strength of 0.005 M. and glycine concentration of 40 Gm./L. These extractions were combined and Fraction II was precipitated in 22 per cent ethanol and 0.071 M. disodium tartrate.[4]

The IV+V precipitate was taken up in 5 ml. distilled water as a cloudy solution and equilibrated with a cationic resin (Dowex 50) to remove the zinc ion, after which a clear solution was obtained. The criterion for sufficient ion exchange was failure of a pink color to develop when 0.25 ml. of the protein solution was mixed with 0.05 ml. of 0.001 M. dithizone in $CHCl_3$. The protein solution was then adjusted to a pH of 7.4 and ionic strength of 0.16 M. by adding 4 ml. to a test tube containing the dried crystals from 0.4 ml. of a solution of 1.5 M. NaCl buffered with 0.1 M. phosphate.

The I+III precipitate was taken up in 5 ml. 0.15 M. NaCl buffered with phosphate at pH 7.4. Fibrinogen was allowed to clot out overnight at 4° C., the residual fraction thereafter being referred to as IIId.† All fractions were

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†The symbol IIId is here used to differentiate this fraction from Cohn's Fraction III, in which the fibrinogen is removed by further treatment with alcohol, rather than simple clotting.

sterilized by Seitz filtration and stored at –10° to –20° C. until used. Fractions were considered "undiluted" when present in the above states, where their protein concentrations were approximately equal to those which they had had in the original unfractionated plasma.

Fraction IV + V is shown electrophorectically to contain the albumin, $alpha_1$ globulin, and about half the $alpha_2$ globulin. Fraction IIId has in addition to the beta globulins some $alpha_2$ globulin and 10 to 20 per cent of the gamma globulins. Fraction II consists only of gamma globulins.

Skin Testing.—Nonreactive, nonragweed-sensitive patients from the allergy clinic were chosen as recipients. Skin sites were prepared with five-fold dilutions of the original plasma and fractions in 0.1 ml. amounts. The sites were carefully marked. Forty-eight hours later the prepared skin sites were each tested with 0.01 ml. of 1:1000 ragweed extract in Coca's fluid.[5] The wheal and flare response was recorded directly by tracing over it on matte-acetate paper.*

Protein Determinations.—All protein concentrations were estimated by the Biuret reaction as modified for quantitative analysis.[3]

TABLE I. PARTITION OF RAGWEED REAGIN AMONG PLASMA PROTEIN FRACTIONS

	WHOLE PLASMA	FRACTION IV + V	FRACTION IIID	FRACTION II
T. S.	625*	125	625	5
A. R.	Not tested	5	25	1
B. R.	25	1	25	Negative
W. O.	25	5	25	1

*Reciprocal of highest dilution showing definite positive passive transfer reactivity.

RESULTS

Table I shows the results of skin testing in all four patients and in Fig. 1 is presented a reproduction of the tracings made on the plasma of T.S. It is clear that the skin-sensitizing antibody of ragweed allergy is concentrated in Fraction IIId. Table II presents the relative proportions of proteins in these fractions as referred to the original plasma.

TABLE II. RELATIVE PROTEIN CONTENTS OF FRACTIONS AND ORIGINAL PLASMA

	PLASMA	IV + V	IIID	II
T. S.	100*	67	21	12
A. R.	100	65	18	17
B. R.	100	70	17	13
W. O.	100	62	23	15

*Expressed as per cent of original plasma.

DISCUSSION

Fraction IIId consists primarily of the beta globulins, while the bulk of the alpha globulins are found with albumin in Fraction IV + V. Our results, therefore, are in accord with those of Campbell, who demonstrated the reagin content of sera separated by the electrophoresis-convection technique to lie principally with the alpha and beta globulins and with the more recent

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work of Cooke and associates[6] who have found passive transfer activity to lie predominantly among the "mid-portion" serum proteins separated by the classical Tiselius electrophoreses.

By an earlier fractionation scheme (Method 6 of Cohn) Enders,[7] and others found that most of the classical antibodies of normal serum lie among the gamma globulins in Fraction II. The somatic agglutinin of the typhoid organism which was in Fraction III was a notable exception to this. The present report would indicate that antiragweed antibody will constitute a second exception, if we can assume that the Fraction II's obtained by the earlier and later fractionation schemes are essentially the same. In addition,

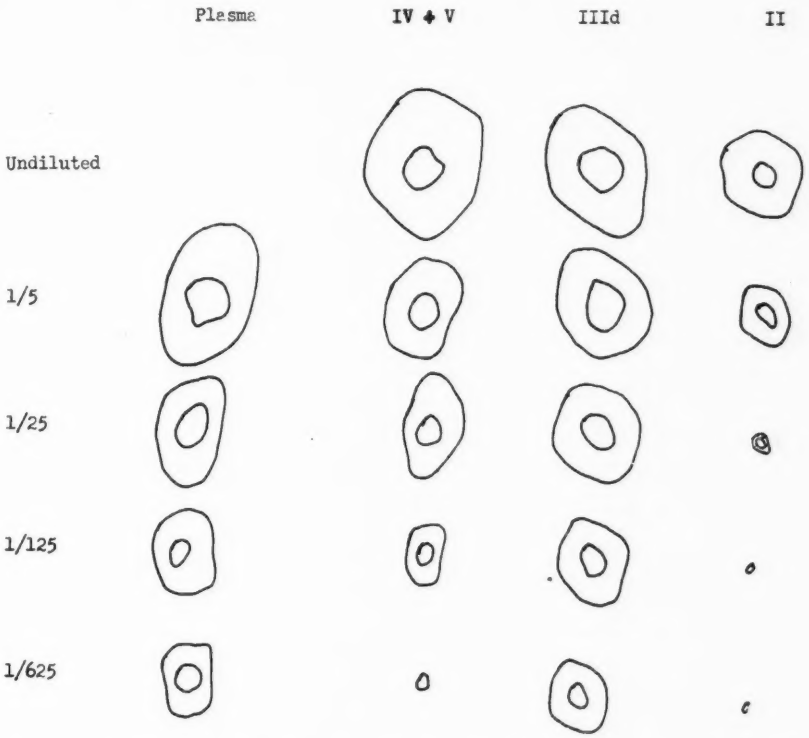

Fig. 1.—Skin sites sensitized with 0.1 ml. and tested 48 hours later with 0.1 ml. 1/1000 ragweed extract in Coca's fluid. Plasma from patient T. S. with ragweed hay fever. (Reduced to ⅔ actual size).

the presence of considerable passive transfer activity in Fraction IV+V, which is essentially free of gamma globulins, is further evidence that antiragweed antibodies are not gamma globulins.

SUMMARY

The skin-sensitizing antibody of ragweed hay fever has been shown to be concentrated among the proteins of Fraction IIId, as separated by alcohol precipitation in the cold.

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INTRAVENOUS ACTH IN THE TREATMENT OF ALLERGIC DISEASES

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THE clinical and experimental use of adrenocorticotropic hormone (ACTH) in the treatment of allergic diseases has been rather extensive since the first clinical ACTH conference in October of 1949 and particularly since ACTH became available for general use in 1950. The majority of reports on ACTH appearing in the literature have been based upon its administration by the intramuscular route and until recently, perhaps even now, the conventional method has been intramuscularly.

The first reports of the intravenous administration of ACTH were by Gordon and his associates[1, 2] in which it was estimated that the cortical response, measured by the increase of ketosteroid excretion and decrease in total blood eosinophils, was up to twenty times greater when ACTH was given intravenously rather than intramuscularly, dose for dose. Forsham, Renolds, and Lesh[3] also reported substantial increase in the excretion of 17-ketosteroids after intravenous ACTH. Mandel and his co-workers[4] reported on twenty-five patients, including eight cases of allergic and collagen diseases, treated intravenously with 1 to 20 mg. ACTH for 8 to 12 hours, and concluded that the therapeutic results were "as good or even better, with only $\frac{1}{10}$ to $\frac{1}{20}$ the doses previously employed intramuscularly in similar cases."

This presentation is a report of the treatment of 60 cases of asthma, urticaria, and allergic dermatitis treated with ACTH intravenously alone or by a combined intravenous and intramuscular method. The study included 35 cases of asthma, 16 cases of urticaria and angioneurotic edema and 9 cases of dermatitis, including atopic or neurodermatitis and contact dermatitis (Table I).

METHODS

1. *Route of Administration.*—All patients received intravenous ACTH (Armour) in one of the following manners: a) *Intermittent:* Daily infusions over a period of 8 to 12 hours for 2 to 10 days were administered to 14 patients. This method was used earlier in this study and was later abandoned in favor of continuous or combined therapy. b) *Continuous:* Continuous infusions from 2 to 5 days were administered to 20 patients. Occasionally the intravenous flow stopped spontaneously from extravasation or the infusion needle "plugged," in which instances the intravenous was re-started, usually at another site, with loss of only a few minutes of continuous flow. (In a few instances the patient complained of great fear of the infusion continuing throughout the first night of therapy and was therefore changed from continuous to intermittent or combined intravenous-intramuscular therapy.) c) *Combined Intravenous-Intramuscular:* Daily infusions lasting 8 to 12 hours combined with one daily intramus-

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TABLE I. METHODS OF ACTH ADMINISTRATION AND NUMBER OF PATIENTS TREATED BY EACH METHOD

	INTRAVENOUS CONTINUOUS	INTRAVENOUS INTERMITTENT	INTRAVENOUS AND INTRAMUSCULAR	TOTAL
Asthma	10	10	15	35
Urticaria	6	2	8	16
Dermatitis	4	2	3	9
Total	20	14	26	60

cular injection for 2 to 10 days were administered to 26 patients. The infusions were given from about 8 A.M. to between 4 and 8 P.M. and the intramuscular injection at midnight.

2. *Dosage.*—Each patient received 10 or 12.5 mg. ACTH per 1,000 c.c. 5 per cent glucose in water, each 1,000 c.c. of fluid requiring 8 to 12 hours for administration. The 12.5 mg. dosage was used in the earlier phase of this study when 25 mg. bottles of ACTH were employed. After 10 mg. bottles were available, 10 mg. was adopted as a routine for all dosages regardless of the method of administration. Those patients in the combined intravenous-intramuscular group received 10 to 12.5 mg. ACTH intramuscularly at midnight in addition to the daily infusion. The continuous intravenous group received a total of 20 to 30 mg. ACTH in 24 hours.

3. *Diet.*—A regular diet, permitting table salt and water as desired, was given all patients except those with other conditions such as heart disease in whom there was danger of inducing sodium and water retention. In a number of instances, however, the patient was changed from a general to a 1 or 2 Gm. salt diet after the appearance of pitting edema, excessive weight gain, or an elevated blood sodium.

4. *Potassium.*—Potassium Chloride, 3 Gm. daily, was prescribed to those patients showing low blood potassium during therapy and to those patients on low sodium diets.

5. *Observations.*—Weight, blood pressure, urinalysis for sugar, and observation for peripheral pitting edema were recorded daily. Fasting blood sugar, sedimentation rate, and blood sodium and potassium determinations were done before and just after the completion of therapy and in some cases during the course of treatment in the majority of the patients.

6. *Total Blood Eosinophil Counts.*—Fasting morning total blood eosinophil counts were performed in all patients. In most cases the counts were done daily. The technique described by Randolph[5] was used.

7. *Ketosteroid Determinations.*—The excretion of 17-ketosteroids per 24 hours was measured in 5 patients, including the periods 24 hours prior to therapy, the first 24 hours of therapy, and the period between 72 and 96 hours of therapy. The method of analysis was a modification of the technique of Holtroff and Koch.[6]

8. *Other Drugs Used.*—Antibiotics, chiefly penicillin and streptomycin, were given to those patients showing significant evidence of active infection, regardless of the type of the allergic disease or the method of treatment with ACTH. The reports of Finland and his co-workers[7, 8] and of Glaser, Berry, Loeb, and

Wood[9] indicate that ACTH (or cortisone) therapy should be accompanied by appropriate antibiotic therapy in all instances where active infection is associated.

RESULTS

The therapeutic response to intravenous ACTH was, in general, excellent, although in most instances only temporary. Only one patient failed to show essentially complete clearing of the symptoms and physical signs of the particular disease before completion of the therapy. This was a case of asthma, complicated by pulmonary emphysema and arteriosclerotic heart disease. Even though there was partial clinical improvement, it appeared that cortical exhaustion may have occurred as evidence by the daily fasting eosinophil count and 17-ketosteroid excretions. Whereas this patient showed a satisfactory 17-ketosteroid excretion after 24 hours of combined intravenous and intramuscular ACTH, there was essentially no further increase in steroid excretion after 96 hours of ACTH (case C. W.).

Whereas it is difficult to evaluate clinical results of any type of therapy in different patients, it appears from this study that the best and most rapid clinical results were obtained with the continuous intravenous method of administration of ACTH. Although the combined intravenous and intramuscular method appeared not to be quite as effective as the continuous infusion, but somewhat more effective than the daily intermittent infusion, the results of this study suggest that it is probably the most practical method of administration.

Total Eosinophils.—Fasting total blood eosinophil counts, carried out on each patient, showed a significant fall in all cases, and in most instances there was a fall of 50 per cent or more after 24 hours of therapy regardless of the method employed. The daily intermittent intravenous method rarely induced a count approaching zero even after several days. The combined intravenous-intramuscular method usually induced counts approaching zero after 1 to 4 days' therapy. It was not uncommon, however, that the continuous infusion induced an eosinophil count approaching zero after one continuous infusion of 20 to 25 mg. ACTH in 24 hours. In one case, the count fell from 880 to zero after one infusion of 10 mg. in 12 hours. These observations are striking in view of findings of Shulman, Harvey, and their associates[10] that the maximum satisfactory fall in total eosinophils occurred between 4.4 and 9.1 days in asthmatics receiving 100 mg. of ACTH per day intramuscularly. Table II is an example of results of eosinophil counts in patients receiving continuous intravenous and combined intravenous-intramuscular therapy.

17-Ketosteroid Excretion Studies.—There was a significant increase in the excretion of 17-ketosteroids in 24-hour urine samples after 24 hours of therapy in each of the 5 cases studied and, with one exception, a still greater increase after 96 hours of treatment. The output was greatest after continuous infusion of ACTH when the values increased from 18.6 to 44.3 after 24 hours and 66.6 mg. per 24 hours after 96 hours of therapy (Table III). With the combined intravenous-intramuscular method, the greatest values were from 13.4 to 24.7 after 24 hours and 33.7 mg. per 24 hours after 96 hours of treatment in one patient and from 16 to 32.9 after 24 hours and 44.3 mg. per 24 hours after 96

hours of therapy in another patient (Tables IV & VII). The least values were from 9.4 to 13.9 after 24 hours and 23.4 mg. per 24 hours after 96 hours of treatment (Table V). In one case (C. W.), age 67, it appeared that cortical

TABLE II. TOTAL BLOOD EOSINOPHIL COUNTS OF PATIENTS TREATED WITH ACTH

CASE	DOSE	NO. OF DAYS	BEFORE	AFTER
	Treatment With Continuous Intravenous ACTH			
H. E.	12.5 mg. per 1000 c.c.	3	875	6
			1325	13
			2145	6
W. M.	12.5 mg. per 1000 c.c.	5	2175	1250
				0
				6
				0
				6
H. R.	10 mg. per 1000 c.c.	4	610	11
				11
				0
				0
M. F.	10 mg. per 1000 c.c.	5	642	0
				0
				0
				22
				0
	Treatment With Combined Intravenous and Intramuscular ACTH			
H. E.	12.5 mg. per 1000 c.c.	4	286	121
				52
	12.5 mg. I.M.			22
				22
H. C.	10 mg. per 1000 c.c.	4	198	125
				56
	10 mg. I.M.			62
				0
C. M.	12.5 mg. per 1000 c.c.	5	156	19
				0
	12.5 mg. I.M.			0
				0
				0
S. W.	10 mg. per 1000 c.c.	4	131	88
				22
	10 mg. I.M.			11
				0

exhaustion occurred. Whereas, there was an increase of 17-ketosteroid excretion from 8.2 to 20.7 after 24 hours, it remained at 21.5 mg. per 24 hours after 96 hours of therapy (Table VI). One patient was treated by the combined intravenous-intramuscular method for 4 days, followed by continuous infusion for 3 days. The 17-ketosteroid excretion values increased from 16 to 32.9 mg. per 24 hours during the first 24 hours of ACTH by the combined method and to 44.3 at the end of 96 hours. The value after the subsequent three-day continuous infusion was increased to 61 mg. per 24 hours (Table VII). These values of 17-ketosteroid excretion appear to be of great magnitude, simulating those reported by Gordon, Kelsey, and Meyer.[1, 2] Venning, Johnson, and Rose,[11] administering ACTH intramuscularly, reported increase in excretion of 17-ketosteroid from 7 to 44 mg. per 24 hours and 5.5 to 26 mg. per 24 hours after 11 and 9 days of ACTH, respectively, in 2 cases, but the increase after the first 24 hours of 100 mg. ACTH in divided doses was only to about 10 mg. per 24 hours in each instance.

TABLE III. CASE H. R., AGE 34, URTICARIA, TREATED BY CONTINUOUUS INTRAVENOUS ACTH

DOSE (24 HR.)	TOTAL DOSE	DIET	WEIGHT		EDEMA		MOON FACIES	SODIUM		POTASSIUM		BLOOD SUGAR	
			B	A	B	A		B	A	B	A	B	A
20 mg. per 2000 c.c.	80 mg.	Gen.	162	169	0	0	+ –	144	145.9	3.8	3.9	98	77

URINE SUGAR		BLOOD PRESSURE		SED. RATE		EOSINOPHILS		17 KETOSTEROIDS (MG. PER 24 HR.)	
B	A	B	A	B	A	B	A	B	A
0	0	120/80	115/70 140/70	10	3	410	11 11 0 0	18.6	44.3 (24 hr.) 66.6 (96 hr.)

TABLE IV. CASE F. N., AGE 26, URTICARIA, TREATED WITH COMBINED INTRAVENOUS AND INTRAMUSCULAR ACTH

DOSE (24 HR.)	TOTAL DOSE	DIET	WEIGHT		EDEMA		MOON FACIES	SODIUM		POTASSIUM		BLOOD SUGAR	
			B	A	B	A	0	B	A	B	A	B	A
I.V. 10 mg. per 1,000 c.c. I.M. 10 mg.	40 mg. 40 mg.	Gen.	139	139	0	0		147.5	147.5	4	4.4	70	68

URINE SUGAR		BLOOD PRESSURE		SED. RATE		EOSINOPHILS		17 KETOSTEROIDS (MG. PER 24 HR.)	
B	A	B	A	B	A	B	A	B	A
0	0	115/65	126/70	6	0	233 242	155 122 111 78	13.4	24.7 (24 hr.) 33.7 (96 hr.)

TABLE V. CASE S. W., AGE 67, ASTHMA, TREATED BY COMBINED INTRAVENOUS AND INTRAMUSCULAR ACTH

DOSE (24 HR.)	TOTAL DOSE	DIET	WEIGHT B	WEIGHT A	EDEMA B	EDEMA A	MOON FACIES	SODIUM B	SODIUM A	POTASSIUM B	POTASSIUM A	BLOOD SUGAR B	BLOOD SUGAR A
I.V. 10 mg. per 1,000 c.c.	40 mg.	2 Gm. NaCl	131	129	0	0	0	144	146	4.8	4.4	77	78
I.V. 10 mg.	40 mg.												

URINE SUGAR B	URINE SUGAR A	BLOOD PRESSURE B	BLOOD PRESSURE A	SED. RATE B	SED. RATE A	EOSINOPHILS B	EOSINOPHILS A	17 KETOSTEROIDS (MG. PER 24 HR.) B	17 KETOSTEROIDS (MG. PER 24 HR.) A
0	0	135/80	150/80	10	2	131	88	9.4	13.9 (24 hr.)
							22		23.4 (96 hr.)
							11		
							0		

TABLE VI. CASE C. W., AGE 67, ASTHMA TREATED BY COMBINED INTRAVENOUS AND INTRAMUSCULAR ACTH

DOSE (24 HR.)	TOTAL DOSE	DIET	WEIGHT B	WEIGHT A	EDEMA B	EDEMA A	MOON FACIES	SODIUM B	SODIUM A	POTASSIUM B	POTASSIUM A	BLOOD SUGAR B	BLOOD SUGAR A
I.V. 10 mg. per 1,000 c.c.	100 mg.	1 Gm. NaCl	141	142	0	+	0	141.9	152.1	5.2	4.7	72	68
I.M. 10 mg.	100 mg.												

URINE SUGAR B	URINE SUGAR A	BLOOD PRESSURE B	BLOOD PRESSURE A	SED. RATE B	SED. RATE A	EOSINOPHILS B	EOSINOPHILS A	17 KETOSTEROIDS (MG. PER 24 HR.) B	17 KETOSTEROIDS (MG. PER 24 HR.) A
0	0	112/70	150/75	6	0	374	341 560	8.2	20.7 (24 hr.)
						385	187 407		21.5 (96 hr.)
							99 220		
							66 308		

TABLE VII. CASE M. R., AGE 29, GENERALIZED ECZEMA, TREATED BY COMBINED INTRAVENOUS AND INTRAMUSCULAR ACTH FOR 4 DAYS FOLLOWED BY CONTINUOUS INFUSIONS OF ACTH FOR 3 DAYS

DOSE 24 HR.		TOTAL DOSE			WEIGHT		EDEMA		Na		K	
I.V. & I.M.	CONT.	I.V. & I.M.	CONT.	DIET	B	A	B	A	B	A	B	A
10 mg. per 1,000 c.c. I.V. 10 mg. I.M.	25 mg. per 2,500 c.c.	40 mg. I.V. 40 mg. I.M.	75 mg. I.V.	Gen.	130 131	132 135 137	0	0 3.7	149/4	144.5 141.9	4.9	3.8

BLOOD SUGAR		URINE SUGAR		BLOOD PRESSURE		SED. RATE		EOSINOPHILS		17 KETOSTEROIDS (MG. PER 24 HOURS)		
B	A	B	A	B	A	B	A	B	A	BEFORE	AFTER COMBINED I.V. & I.M.	AFTER CONTINUOUS I.V.
48	114 (1 hr. after I.V.)	0	0	120/70	130/70 140/90 120/60 160/70 130/70 145/60	14	4	737 1166	132 33 22 143 0 0 44	16	32.9 (24 hr.) 44.3 (96 hr.)	61 (72 hr.)

TABLE VIII. SIDE EFFECTS OF INTRAVENOUS ACTH

CASE	EDEMA	WEIGHT		SODIUM		POTASSIUM		METHOD	BLOOD PRESSURE		DIET
		B	A	B	A	B	A		B	A	
W. H.	2+	100	114	136	147	4.6	2.9	Cont.	132/90	160/100	Gen.
S. M.	1+	151	159	152	148	3.6	3.2	Comb.	100/80	140/70	Gen.
M. F.	+	151	156	143	150	4.6	3.4	Cont.	100/80	140/100	Gen.
W. M.	+	142	148	148	147	4.0	2.7	Cont.	140/90	150/90	Gen.
C. W.	+	141	142	142	152	5.2	4.7	Comb.	112/70	150/75	1 Gm. NaCl
M. P.	1+	150	155	---	---	---	---	Comb.	110/60	120/70	Gen.
S. E.	+	152	161	---	---	---	---	Comb.	120/80	120/60	Gen.
C. M.	0	113	121	151	147	5.2	4.4	Comb.	118/80	110/80	Gen.
S. W.	0	140	148	144	150	4.5	3.6	Comb.	130/70	130/60	Gen.
H. E.	0	139	150	147	146	3.8	4.9	Cont.	145/90	170/100	1 Gm. NaCl

Cont.—Continuous Intravenous.
Comb.—Combined intravenous and intramuscular.

Weight and Edema.—A gain in weight was quite common and occurred in the majority of the patients on a general diet, regardless of the change in blood sodium and potassium or demonstrable peripheral pitting edema. Furthermore, there was weight gain in some patients, such as case H. E. (Table VIII), who was on a diet of 1 or 2 Gm. of salt per day, and in whom no edema developed and no significant change occurred in the blood sodium and potassium levels. Whereas the weight gain in some cases appeared to be due to sodium and water retention, in others it seemed to be due to increased appetite and caloric intake as a result of ACTH therapy. Demonstrable pitting edema occurred in only 7 patients. Cessation of ACTH therapy resulted in diuresis and a loss of all or part of the weight gain and the edema when present (Table VIII).

Electrolytes.—An increase in blood sodium and a fall in blood potassium were not uncommon in this study but the values rarely varied beyond the extreme limits of normal even when the patient was on a general diet.

Blood Pressure.—There was a general tendency for a rise in blood pressure after intravenous ACTH but in no instance was the increase alarming, even when the patient was on a general diet.

Blood Sugar.—In no instance was there a significant rise in the fasting blood sugar value after ACTH therapy.

Urine Sugar.—In only one instance was there demonstrable glycosuria and that was minimal and occurred in only one specimen, immediately after which ACTH therapy was discontinued.

Sedimentation Rate.—There was a general tendency to a fall in the sedimentation rate values, even when the pre-treatment values were normal.

Tables III to VIII show examples of weight gain with and without pitting edema, blood sodium and potassium values, blood pressure observations, blood sugar, urine sugar, and sedimentation rate determinations before and after ACTH therapy.

COMMENT

The clinical observations and laboratory studies including total blood eosinophil counts and 17-ketosteroid excretion, carried out in this series of 60 patients with allergic diseases, treated with adrenocorticotropic hormone administered intravenously either once daily, continuously for several days, or once daily combined with one daily intramuscular injection approximately midway (at midnight) between the daily infusions indicate the advantages of intravenous therapy over the conventional intramuscular method of administration of this hormone. The first advantage is the increased efficiency of therapy as manifested by a more rapid relief of symptoms and the clearing of the physical signs when the doses used were much smaller than usually given intramuscularly. The second advantage is the economy of its use. ACTH is relatively expensive when given in doses of 25 mg. or more intramuscularly every six hours. Whereas 10 to 12.5 mg. (most cases received 10 mg.) have been the standard dosage used in this study for sake of consistency, it is highly possible that 5 mg. or even 1 mg. intravenously may be effective as suggested by Gordon.[12]

No attempt was made in this study to gradually reduce the dosage of ACTH before cessation of therapy. Several patients, therefore, developed a post-

treatment syndrome of exhaustion, manifested chiefly by weakness and lightheadedness 2 to 5 days after therapy was discontinued. These symptoms were readily controlled by cortisone orally in a gradually decreasing dosage of 25 mg. every 6 hours for 2 or 3 days, every 8 hours for 2 or 3 days, every 12 hours for 2 or 3 days and then once daily for 2 or 3 days.

Several additional patients, mostly emergencies not included in this report, in whom laboratory data before and after therapy were not recorded, have been treated by continuous infusion or by the intravenous-intramuscular method with ACTH combination technique in which the infusion was given continuously until the emergency state had subsided, followed by one infusion daily and one intramuscular injection nightly. In these cases, rather than reducing the dosage of ACTH gradually over a period of days to prevent the posttreatment exhaustion phenomenon, cortisone orally was prescribed in the gradually decreasing dosage regimen described above. Such post-ACTH oral cortisone therapy was usually carried out on an out-patient basis, thereby saving hospital days. The addition of aminophylline and sodium iodide to the intravenous fluids containing ACTH did not seem to interfere with the effectiveness of the ACTH.

The intravenous method is practical only for use in hospitalized patients, but once the patient is hospitalized, it is recommended that intravenous rather than intramuscular therapy be used. It is also recommended that an attempt be made to administer the ACTH by continuous infusion in severe or emergency cases for the period of the emergency after which the daily intermittent infusion or the combined intravenous and intramuscular method may be substituted.

It is further recommended that the sodium intake of the patient be reduced while receiving ACTH intravenously if heart or kidney disease or other diseases predisposing to electrolyte imbalance and edema are present, if edema should develop during ACTH therapy or if the patient gains an unusual amount of weight. Daily weight and blood pressure recordings should be made. Fasting blood sugar and blood sodium and potassium determinations should be carried out, if available.

Intravenous or combined intravenous-intramuscular ACTH therapy is, in general, effective in the temporary relief of the allergic state, but it is not a substitute for specific antiallergic diagnosis and therapy and the causative agent or agents must be eliminated or the patient treated accordingly such as hyposensitization as pointed out by Cooke and his associates,[13] Feinberg and his co-worker,[14] and others.

CONCLUSIONS

1. Clinical and laboratory studies on 60 patients with asthma, urticaria and allergic dermatitis treated with corticotropin (ACTH) administered intravenously or by a combined intravenous and intramuscular method have been presented.

2. The clinical response, fasting total eosinophil counts and 17-ketosteroid excretion studies indicate a great advantage of ACTH given intravenously or combined with intramuscular administration over the conventional intramuscular use of the hormone.

3. The effects of intravenous ACTH therapy upon weight and edema, blood pressure, blood sodium and potassium, blood and urine sugar values and the sedimentation rate are presented.

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NEUTRALIZING ANTIBODY IN NONALLERGIC INDIVIDUALS

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IN EXTENDING our studies[1, 2] on the effect of treatment of ragweed pollinosis with modified extracts one of the criteria it was planned to employ in the choice of material was the neutralizing antibody produced in nonallergic individuals in response to the administration of the extract. When the titers were determined it was found that the results gave us no basis for the selection of extracts. Nevertheless, these findings were deemed of interest because they furnished substantial data of the effect of pollen injections on the neutralizing antibody formation in nonallergic people.

EXPERIMENTAL

Extracts.—A series of eight different ragweed pollen extract preparations were compared for their effectiveness in antibody production. The preparation and rationale for the use of each are as follows.

1. Aqueous ragweed extract. This extract, which served as a control, was that commonly used in this laboratory in desensitization therapy. Mixed ragweed pollen was extracted with water in the ratio of 3 Gm./100 ml., dextrose and phenol added to 5 per cent and 0.5 per cent concentration, respectively, and sterilized by Seitz filtration. One milliliter of this extract contained approximately 15,000 protein nitrogen units (PNU).

2. Dialyzed aqueous extract. Three per cent pollen extract prepared as above was dialyzed in the cold room for 28 hours with three changes of distilled water. Dextrose and phenol were added to a 5 per cent and 0.5 per cent concentration, respectively, and sterilized by Seitz filtration. It has been observed[3, 4] that dialysis of ragweed extract removes some of the components which produce the local reaction. The low molecular weight fractions which are removed by dialyzing may have had the capacity of diminishing the antigenicity of the higher molecular weight components.

3. Alum precipitated ragweed extract. Five hundred milliliters of 3 per cent pollen extract was concentrated to 400 ml. in vacuo and Seitz filtered into 75 ml. of sterile 10 per cent potassium alum solution. To each 10 ml. of the above solution the addition of 0.24 ml. of sterile 4 normal sodium hydroxide brought the final pH to between 6.5 and 7.5. Alum precipitation has been utilized for a long time where delay in absorption of an antigen was desired.

4. Tannic acid precipitated extract. A sterile solution of 500 ml. of 3 per cent pollen extract which had been concentrated in vacuo to 160 ml. was added to 40 ml. of sterile 5 per cent tannic acid solution. After the precipitate had

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been allowed to settle overnight in the cold room, the supernatant was decanted and the precipitate was washed three times with sterile 95 per cent ethyl alcohol. The precipitate was then suspended in 500 ml. of isotonic saline containing 0.5 per cent phenol. Naterman[5, 6] has reported excellent results by treating patients with extracts similarly prepared.

5. Extract containing 10 per cent polyvinylpyrrolidone. Five hundred milliliters of 3 per cent pollen extract was concentrated in vacuo to 360 ml., 4.5 Gm. of sodium chloride and 2.5 Gm. of phenol were added and the solution sterile-filtered into a flask containing 140 ml. of an autoclaved aqueous 35.7 per cent solution of polyvinylpyrrolidone bringing the final concentration to 10 per cent. Polyvinylpyrrolidone solutions have been reported[7] as being effective in delaying the absorption of certain biologicals such as the adrenocorticotrophic hormone.

6. Pertussis vaccine incorporated extract. Pollen extract was concentrated as previously described from a volume of 500 ml. to 360 ml. To the sterile concentrate was added 140 ml. of Sharp and Dohme Pertussis Vaccine Suspension. The use of particulate matter as a "schlepper" is an acknowledged procedure in the enhancement of antigenicity.

7. Two per cent sodium gentisate containing extract. Enough sodium gentisate was added to a 3 per cent dextrose-phenol extract of pollen to make a 2 per cent solution. Sodium gentisate has been reported[8] as being an hyaluronidase inhibitor and thus, perhaps, a deterrent to absorption.

8. Aluminum monostearate-oil extract. Seven hundred fifty milliliters of 3 per cent pollen extract was concentrated to 500 ml. and Seitz filtered into 225 ml. of sterile 20 per cent soluble starch solution. The solution was frozen immediately, lyophilized aseptically, and the dry solids suspended in 750 ml. of sterile sesame oil containing 2 per cent aluminum monostearate and 0.5 per cent chlorobutanol. A sterile colloid mill was used to suspend the lyophilized solids. The delay in absorption of penicillin from such a depot has been observed clinically.

Immunization Schedule.—Blood serum samples were taken before the initiation of treatment from a total of 36 normal volunteers not sensitive to ragweed pollen. Three to five subjects were immunized with each separate preparation. Weekly subcutaneous inoculations were given in the upper arm commencing with a 0.25 ml. dose, increasing to 0.50 ml. for the second injection with subsequent 1.0 ml. doses for the duration of the experiment. Twenty-six inoculations in all were given totaling approximately 371,250 PNU. Blood serum samples were taken one week after the thirteenth and twenty-sixth injections. Treatment with preparation No. 8 (ragweed aluminum monostearate-oil extract) which had been given intramuscularly was stopped after the thirteenth injection because of local induration and pain. None of the other preparations caused any local discomfort serious enough to warrant its discontinuance.

Neutralizing Antibody Titration.—The technique of Loveless[9] was used essentially as described with certain minor modifications. Using sterile precautions an equal volume of undiluted experimental serum was added to increasing dilutions of aqueous ragweed pollen extract. The mixture was incubated at

TABLE I. REACTIONS TO RAGWEED ANTIGEN OF SITES PASSIVELY SENSITIZED TO VARIOUS MIXTURES OF REAGIN, EXPERIMENTAL SERUM, AND RAGWEED EXTRACT

RAGWEED DILUTIONS	RAGWEED EXTRACT + PRE-TREATMENT SERUM + REAGIN		RAGWEED EXTRACT + SALINE SOLUTION + REAGIN		RAGWEED EXTRACT + POSTTREATMENT SERUM + REAGIN	
	TECHNIQUE		TECHNIQUE		TECHNIQUE	
	REMOTE	DIRECT	REMOTE	DIRECT	REMOTE	DIRECT
			Subject: G. L.			
Saline Solution	++++		++++		++++	
1:243,000	++++		++++		++++	
1:81,000	++++		++++		++++	
1:27,000	++		++		++	
1:9,000	−		−		−	
1:3,000	−	+++	−	+++	−	+++
1:1,000*	−	+++	−	+++	−	+++
1:300		++		++		+
1:100		−		−		−
1:33.3		−		−		−
Controls						
Saline Solution + Pretreatment serum + Ragweed diluted 1:1000			−			
Saline Solution + Posttreatment serum + Ragweed diluted 1:1000			−			
Saline Solution + Pretreatment serum + Saline Solution			−			
Saline Solution + Posttreatment serum + Saline Solution			−			
			Subject: P. K.**			
Saline Solution			++++		++++	
1:243,000			++++		++++	
1:81,000			++++		++++	
1:27,000			++		++++	
1:9,000			−		++	
1:3,000			−		++	
1:1,000*			−		++	
1:300			−		−	
1:100			−		−	
1:33.3			−		−	
Controls						
Saline Solution + Posttreatment serum + Ragweed diluted 1:1000			±			
Saline Solution + Posttreatment serum + Saline Solution			±			

*1 ml. 1:1000 = 500 PNU.

**Serum heated at 58° C. for 1 hour before testing.

Technique: Equal parts ragweed extract and experimental serum mixed and incubated for 10 minutes at 37° C. One-half volume reaginic serum added and mixed. Skin sites passively sensitized with 0.1 ml. of mixture and tested after 48 hours.

Remote testing: 1 ml. of 1:10 ragweed extract injected s. c. Sites read after 60 minutes

Direct testing: Each site inoculated with 0.025 ml. of 1:1000 ragweed extract and read after 10 minutes.

40° C. for about 15 minutes following which one volume of undiluted reaginic serum was added; each of the reagents was thus diluted 1:3. This mixture was stored in the refrigerator before use for a maximum of 24 hours. Suitable controls were prepared for reaginic and experimental sera. Sites were sensitized on the backs of nonsensitive volunteers using 0.1 ml. of each mixture. Immediate-reaction readings were taken ten minutes after sensitization. About 48 hours after sensitization the passively sensitized sites were challenged by either the remote or direct technique. In the former procedure, 1 ml. of a 1:10 concentration of aqueous ragweed extract was administered subcutaneously. Readings at the previously sensitized sites were taken after 60 minutes. In the latter procedure, each site was directly challenged by the injection of 0.025 ml. of 1:1000 concentration of aqueous ragweed extract. Results were recorded at 10 minutes. The sera of all the subjects were titrated by the remote and seven of the sera by the direct technique.

As a titration control, serum from an extensively treated ragweed sensitive patient (P. K.) known to have a relatively high neutralizing antibody titer was included in the above studies.

RESULTS

Typical protocols for the remote and direct techniques are shown in Table I of the data for volunteer G. L., and ragweed-sensitive patient, P. K. In none of the 36 subjects tested by either of the procedures described was there any increase in neutralizing antibody which was considered as being significant and beyond the scope of experimental error. For example, the serum of an occasional subject titered to a difference of a single multiple ragweed dilution of 1:3: reagin containing pretreatment serum, L. M. K., neutralized a ragweed dilution of 1:9,000; with posttreatment serum, 1:3,000, thus a difference of 165 PNU/ml. is represented.

DISCUSSION

The literature contains undisputable reports[9-25] that an antibody is produced in pollen sensitive patients in response to the usual course of treatment with specific antigen. This antibody has been termed "blocking" or, preferably, "neutralizing" because of its more rapid capacity to bind the antigen than the skin sensitizing antibody or reagin.

The acceptance that the parenteral administration of nonpollen sensitive individuals with an arbitrary amount of pollen extract over an indefinite period of time also results in the production of an identical serologically specific antibody is based on relatively few reports.[9, 25-27] Unsuccessful attempts to demonstrate this antibody in response to such stimulus are recorded also.[11, 25-27] A compilation of the literature indicates that in 9 out of a total of 14 individuals there were no appreciable amounts of antibody. In addition, Fitzgerald and Sherman[25] have indicated that specific antibodies to grass pollen extract were demonstrated in 4 out of 6 nongrass-sensitive patients who had other manifest allergies but were treated with grass pollen extract.

Remote testing: 1 ml. of 1:10 ragweed extract injected s. c. Sites read after 60 minutes
Direct testing: Each site inoculated with 0.025 ml. of 1:1000 rag weed extract and read after 10 minutes.

The obvious difference between the requirement of the sensitive and nonsensitive individual to produce neutralizing antibody seems to manifest itself in the amount of pollen extract which need be administered.

It seems apparent that under the regime of preseasonal treatment which the usual pollen sensitive patient undergoes the nonsensitive individual will produce no detectable neutralizing antibody. This observation is supported by the results of the present study in which essentially little or no antibody was formed after the administration of about 370,000 PNU. This amount of extract is actually much more than is commonly given as treatment to a pollen sensitive individual in a single season. It has usually required much greater amounts of extract, usually well over 500,000 PNU to stimulate the production of neutralizing antibody, although it has been detected[26] in appreciable titer in a nonatopic individual receiving 211,000 PNU. On the other hand, "relatively little humoral" antibody was detected in a volunteer who had received as much as 2,162,500 PNU.[27] Follensby[28] also has not been able to demonstrate more than small amounts of neutralizing antibody in 2 out of 3 volunteers treated with ragweed extract. The amount of antibody produced in the third subject was equivalent to less than 2,000 PNU/ml. of serum and resulted from the administration of about 800,000 PNU given over a period of approximately 5½ months.

The time relationship appears to be less significant, for neutralizing antibody has been reported three weeks after the start of treatment.[6] In our experience 26 inoculations were given over as many weeks without more than a questionable increase in the titer of neutralizing antibody.

Two of the experimental extracts were used in desensitization therapy in several patients during the past ragweed pollen season of 1951 but the series was considered to be too small to allow for any justifiable conclusion as to efficacy of treatment. Also, it is not within the scope of this paper to discuss the relationship between neutralizing antibody titer and efficacy of treatment.

SUMMARY

Neutralizing antibody titrations were carried out in series of nonatopic human volunteers receiving one of the following ragweed preparations: (1) aqueous, (2) dialyzed aqueous, (3) alum precipitated, and (4) tannic acid precipitated extract. Also, extracts were made up to contain one of the following: (5) 10 per cent polyvinylpyrrolidone, (6) pertussis vaccine and (7) 2 per cent sodium gentisate. Number 8 was a preparation in an aluminum monostearate-oil menstruum. A total of over 370,000 PNU of ragweed extract was administered during the course of 26 weekly injections. No significant increase in neutralizing antibody was detected after such a series of injections.

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TRANSITORY PULMONARY INFILTRATIONS WITH BLOOD EOSINOPHILIA OF EIGHTEEN MONTHS' DURATION TREATED WITH CORTISONE

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THE favorable response to pituitary adrenocorticotrophic hormone (ACTH) in a case of Loeffler's syndrome reported by Herbert, DeVries, and Rose[1] at the Fifth Annual Meeting of the American Academy of Allergy in Atlantic City on December 6 to 8, 1948, and subsequently reported in this journal, suggested the use of cortisone in this case. Although there is a marked difference in the extent and severity of the clinical course between this case and Loeffler's syndrome, there is a similarity of pulmonary lesions and the presence of blood eosinophilia.

CASE REPORT

R. S., a 16-year-old female student, was admitted to the Brooklyn Thoracic Hospital on Dec. 29, 1948, complaining of cough, fatigue, night sweats, and a low grade fever of two months' duration. Previously, for a period of four years, every winter the patient had complained of a persistent dry cough accompanied by occasional mild wheezing of the chest and perennial nasal symptoms of watery nasal discharge, sneezing, and nasal obstruction. There was no loss of weight, anorexia, or hemoptysis. X-ray of the chest on Nov. 9, 1948, revealed pulmonary parenchymal involvement suspicious of tuberculosis. On November 12 the white blood cell count was 9,400 and the blood eosinophils 5 per cent. The sedimentation rate was 12 mm./hr. Further x-rays taken on December 2 and December 23 (Fig. 1) showed resolution of previous areas of pulmonary infiltration and the appearance of new ones.

Physical examination at that time showed a thin but well-developed, energetic female. The temperature was 99.6° F., pulse 90, respiration 20, blood pressure 128/72, weight 121 pounds. Her face was slightly flushed; the skin was moist and showed some tendency to hirsutism. The nasal septum was markedly deviated to the left and the nasal mucous membrane was pale and edematous. Examination of the chest revealed a few scattered sibilant râles at both bases. The heart was not enlarged to percussion and the sounds were regular and of good quality. P_2 was louder than A_2. No murmurs were audible. Hirsutism was present on the chest, back, abdomen, and lower extremities.

X-ray of the chest on the day of admission to the hospital, December 29 (Fig. 2) showed both costophrenic sinuses and diaphragms intact. The heart was normal in size, shape, and position. The right and left lung fields were sites of recent infiltrative changes. Subsequent x-rays (Fig. 3 and Fig. 4) showed resolution of previous areas and the appearance of new areas of infiltration. The x-ray diagnosis was Loeffler's syndrome.

Examinations of several specimens of concentrated sputum were made and found to be negative for acid-fast bacilli and ova. A smear made from the sputum was examined for eosinophils and none were found at this time. A culture of the sputum revealed gamma streptococci, pneumococci, *M. catarrhalis*, and *B. Pfeifer* in moderate numbers, and no acid-fast bacilli. Gastric washings were negative for acid-fast bacilli. Blood count: R. B. C. 4,776,000, hemoglobin 87 per cent, W. B. C. 10,600, polymorphonuclears 59 per cent, small lymphocytes 23 per cent, large mononuclears 8 per cent, eosinophils 10 per cent. Sedimentation rate was 15 mm./hr., and the urine was negative throughout.

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TABLE I. TRANSITORY PULMONARY INFILTRATIONS WITH EOSINOPHILIA. LABORATORY FINDINGS.

DATE	HGB. (PER CENT)	W. B. C.	EOS. (PER CENT)	SED. RATE (MM./HR.)	WT. (LBS.)
11/12/48	—	9,400	5	12	—
12/29/48	87	10,600	10	15	121
2/ 1/49		12,500	20		
2/26/49	75	8,800	22		
3/ 5/49		14,500	20		
3/15/49		17,000	22	42	
3/25/49		20,000	25		
4/10/49	70	25,000	22		
4/20/49	70	25,000	22		
5/ 1/49	68	22,000	24		
8/29/49	88	10,900	2		
9/10/49	80	15,400	10		
10/20/49	66	12,700	19	72	81
10/24/49		5,000	7	40	
11/16/49			14	52	91
12/11/49			21	55	
1/ 1/50			19	51	93
2/ 3/50	75	12,650	10	45	89

While in the hospital the patient was placed on bed rest and remained in the hospital for 28 days. At no time did she appear acutely ill. There was no evidence of weight loss and her appetite was good. On several occasions there was a slight elevation of temperature, up to 100.6° F. and a pulse rate between 90 and 100, even when the temperature was normal. For the most part the temperature remained normal. The cough was persistent and dry, and except for the first two sputum specimens, it was impossible to obtain any sputum for further examination. Several injections of 0.5 c.c. epinephrine 1-1,000 were given without altering the size of the pulmonary infiltrations as observed by x-ray. She was discharged on Feb. 24, 1949, and confined to bed at home. The cough increased in severity and became more persistant. For two weeks she ran an evening temperature between 100.4 and 101° F., and the pulse rate ranged between 110 and 140. X-ray of her chest on Feb. 20, 1949 (Fig. 5) showed in addition to the areas of pulmonary infiltration, atelectasis of the left lung with displacement of the heart to the left. Following this episode, for a period of ten weeks, the temperature ranged between 99.6 and 104.5° F., and the pulse rate between 110 and 150.

TABLE II. EFFECT OF THE AMINISTRATION OF CORTISONE TO A PATIENT WITH TRANSITORY PULMONARY INFILTRATIONS

	CONTROL	CORTISONE				
		3RD DAY	6TH DAY	10TH DAY	14TH DAY	23RD DAY	30TH DAY
Hgb. %	75%						75
R. B. C.	3,780,000						3,350,000
W. B. C.	12,650	12,000	12,200	12,500	12,200	12,000	12,200
Polymorphs %	57					64	71
Lymphocytes %	32					35	27
Eosinophils %	10	0	0	1	2	1	2
Sed. rate mm./hr.	45	45	42		15	12	11
Blood chlorides	453		493			567	529
Blood sodium	321		331		332	341	351
Blood potassium	17.5		17.7		17.2	19	19.6
Blood CO_2	67		66				67
Sugar	79		93		90	107	101
Urea N.	11.6		11.6		14	12.6	16.3
Uric acid	2.51		2.5		1.9		2.0
Creatinine	1.5		1.4		1.5	1.4	1.7
Protein, tot.	6.8		6.95		6.6		6.6
Serum albumin	5.0		4.7				5.1
Serum globulin	1.8		2.25				1.5
Cholesterol total	163		166				188
Cholesterol esters	97						99

Vomiting occurred frequently and she began to show a moderate pallor and became somewhat emaciated. X-ray of the chest during this period again showed the appearance of new areas of infiltration and resolution of previous ones (Fig. 6).

Further laboratory examinations showed the following findings: Eight blood counts taken between Feb. 1 and May 1, 1949, showed a white blood cell range between 8,800 and 25,000; eosinophils between 20 per cent and 25 per cent; hemoglobin from 75 to 68 per cent (Table I). The cough became productive again and two sputum examinations were again negative for acid-fast bacilli. Culture of the sputum showed hemolytic streptococci, *Staphylococcus albus* and *aureus*, pneumococcus (not typed), and *Micrococcus catarrhalis*. Examination of the sputum and nasal smears showed many eosinophils on two occasions. Culture of the nasal secretions revealed *Staphylococcus albus* and hemolytic streptococci. Washings from the sinuses on March 5, 1949, revealed no frank pus and on culture showed pneumococcus Type XII, *Staphylococcus albus* and hemolytic streptococcus, and on smear, many eosinophils. Transillumination of sinuses was negative for sinusitis. Repeated examination of the urine revealed no abnormalities. Three consecutive specimens of stool were negative for ova and parasites. Three blood cultures were negative. The tuberculin test (Mantoux), –0.01 mg. and 1.0 mg., was negative. The intracutaneous tests to the common allergens showed mild reactions to onion, pea, carrot, apple, and cotton seed; moderate reactions to egg, orris, house dust, hormodendron, and alternaria. Known clinical allergens were banana, tomato, pineapple, cheese, spinach, and crab. The patient thought that the ingestion of these foods made her nasal symptoms and cough worse. Intracutaneous tests to ascaris, coccidioidin, and trichiniasis were negative. Serologic examinations, such as the Wassermann, Weil Felix, Richettsia virus, Heterophile, *Brucella abortus*, and cold agglutination were negative. The basal metabolic rate on March 5 was plus 13. Biopsy from the deltoid region on February 28 did not show any evidence of periarteritis nodosa or trichiniasis.

During this period the treatment consisted of the administration of aqueous penicillin, 50,000 units every four hours. The patient was sensitive to penicillin and developed a diffuse urticaria so it had to be discontinued. Aureomycin orally and by aerosol was also given without results. Daily intramuscular injections of 0.5 Gm. of dihydrostreptomycin for two weeks produced no response. The following drugs were also given without results: epinephrine, aminophylline, Pyribenzamine, Neo-hetramine, salicylates, liver extract, iron, vitamins, intravenous Amigen infusions, and one intravenous injection of Mapharsen. It seemed that the antihistamines increased her tachycardia. Following the intravenous injection of Mapharsen she developed a temperature of 105° F. and diarrhea.

During a period of four months, from March to July, 1949, the patient lost about 30 pounds, ran a continuous temperature between 101° and 103° F., tachycardia between 110 and 130, and several nodules were palpable on the left side of the forehead and on the left chest wall. She also complained of weakness and joint pains, and developed a moderate pallor. Petechiae were noted on the fingers and forearms. In July, 1949, pain developed along the lateral aspect of the left foot and numbness of the right side above the iliac crest. Several small petechiae were also noted on the buccal mucosa. Following two blood transfusions, the hemoglobin rose to 88 per cent. Seven weeks later it had fallen to 66 per cent. In September, 1949, examination revealed a heart rate of 130, gallop rhythm, and transient fibrillations. On Sept. 14, 1949, x-ray of the chest (Fig. 7) showed that the cardiac shadow presented a mitral configuration and the heart was enlarged in all its diameters. Both lung fields were well aerated. The electrocardiographic tracings on May 6, 1949 (Fig. 8a), showed sinus tachycardia and right axis deviation, and on Sept. 14, 1949, showed right ventricular strain and toxic myocarditis (Fig. 8b). With digitalization the gallop rhythm disappeared. Examination of the urine showed a 1 to 2 plus albumin and many granular casts. Biopsy and microscopic examination of a nodule removed from the left chest wall revealed nonspecific inflammatory changes. The bone marrow revealed normal cellular marrow, marked increase in the number of eosinophils and no lupus erythematosus cells. X-ray of the sinuses, and also of the gastrointestinal tract, were negative. The electrocardiographic tracings in October of 1949 showed sinus tachycardia and right bundle branch block.

Fig. 1.

Fig. 2.

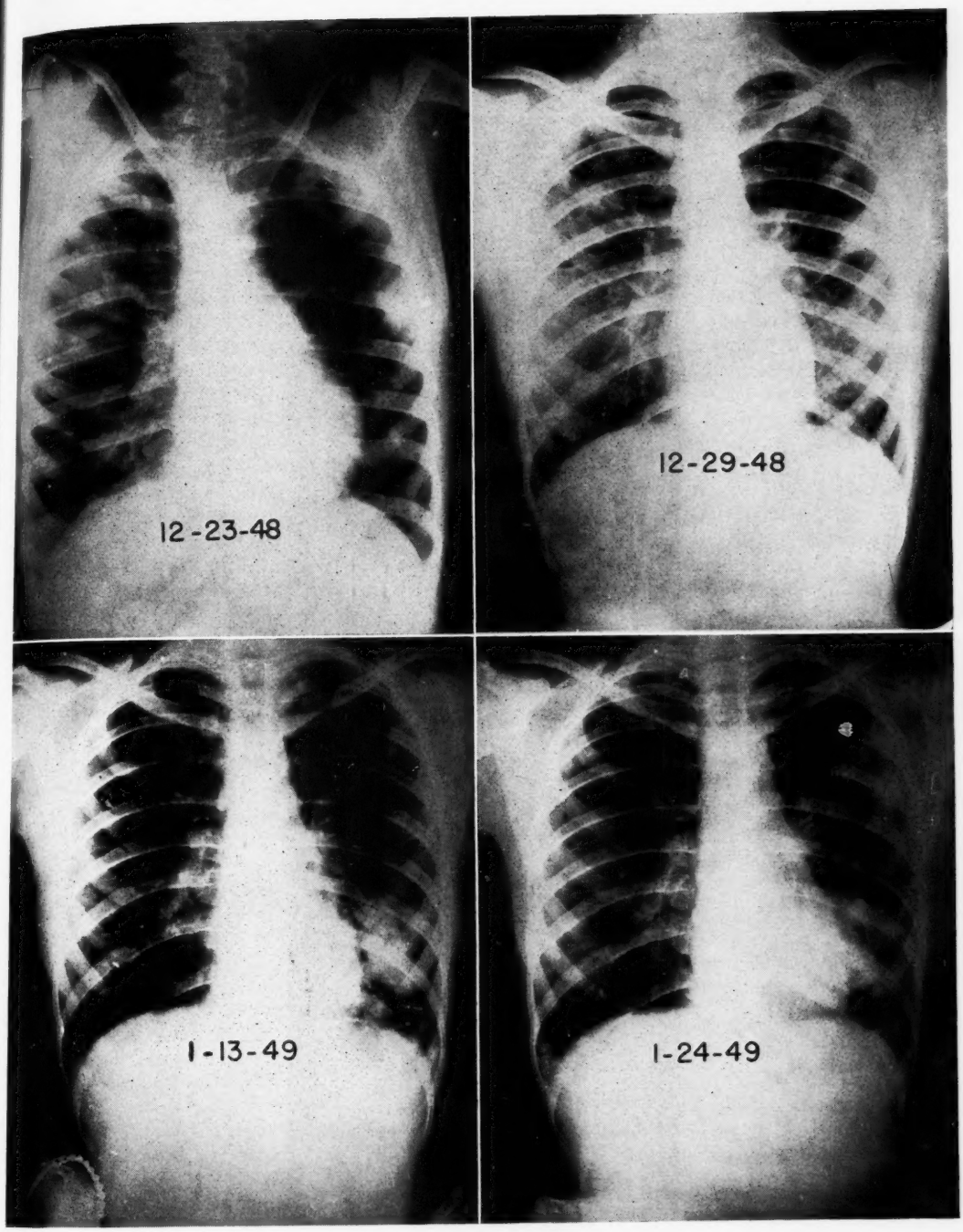

Fig. 3.

Fig. 4.

Fig. 1.—12/23/48. Infiltration, right upper and middle lung field and left middle lung field laterally and inferiorly.

Fig. 2.—12/29/48. The right lung field infiltrate has become harder. The left lung field infiltrate has extended.

Fig. 3.—1/13/49. Large area of infiltration, left lower lung field, with clearing of left upper lung field. Small infiltration, right lower lung field laterally. Recent infiltration at both pulmonary apieces.

Fig. 4.—1/24/49. Further resolution of infiltration throughout the left lung field.

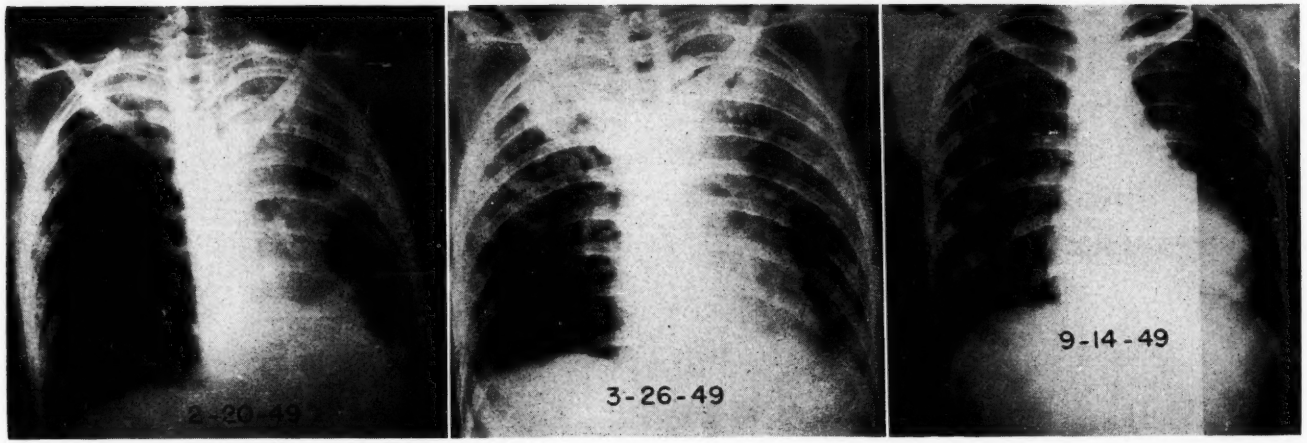

Fig. 5. Fig. 6. Fig. 7.

Fig. 5.—2/20/49. Extension of infiltration and atelectasis throughout entire left lung and extension of infiltration in the right upper lung field.

Fig. 6.—3/26/49. Further extension of right upper lung field infiltration with some resolution of the infiltrate on left side and of the atelectasis on the left side.

Fig. 7.—9/14/49. Both lung fields well aerated. Cardiac silhouette approximately twice original size.

On Oct. 20, 1949, while at Mt. Sinai Hospital, the first course of cortisone was given. She received 150 mg. daily for 8 days, 50 mg. for 6 days, and 25 mg. for 8 days. One week after the onset of cortisone therapy the patient was subjectively improved. The neuritic pain had subsided, and while on cortisone, the patient's weight increased from 81 to 91 pounds and the temperature dropped to 99.4° F. During this time there was also a marked clearing of the lungs as shown by x-ray. On 25 mg. of cortisone the patient's temperature rose slightly. Because of the lack of supply, cortisone had to be discontinued at this time. Daily injections of DOCA solution were then given in doses of 10 mg. intramuscularly in conjunction with 500 mg. of ascorbic acid intravenously. This was given for 12 days without relief. Fever, tachycardia, cough, weakness, and anorexia recurred.

She was discharged and confined at home for five weeks during which time she was acutely ill. The temperature ranged between 101° and 104° F., the pulse rose and ranged between 130 and 160. With no evidence of penicillin sensitivity at this time, 7 injections of 600,000 units of procaine penicillin in aqueous suspension were given with no effect. On Feb. 3, 1950, x-ray of the chest (Fig. 9) showed a recurrence of the transient and migratory solid areas of pulmonary infiltrations. There was a blood eosinophilia of 10 per cent and the sedimentation rate was 45 mm./hr. (Table 1). The electrocardiographic tracings on Feb. 3, 1950, showed a right bundle branch block (Fig. 10).

The second course of cortisone was started on Feb. 3, 1950. Within 24 hours after the initial daily dose of 200 mg. of cortisone the temperature dropped suddenly from 103.4° to 99.4° F., and the pulse rate dropped from 160 to 90. This is shown graphically in Fig. 11. The daily dose of cortisone was gradually decreased until a maintenance dose of 50 mg. every other day was given. On this dosage schedule the following changes have taken place: the temperature ranged between 97.6° and 100.4° F., but for the most part remained normal; the pulse rate ranged between 66 and 108; the appetite increased fourfold, and as a result, there was a gain of 16 pounds, from 89 to 105 pounds; the joint pain disappeared and the cough subsided considerably. Forty-eight hours after the onset of cortisone therapy the patient was out of bed, became active, and felt strong enough to act as a nurse for her mother who was ill.

The eosinophil count dropped in 72 hours from 10 per cent to 0, and during therapy ranged between 0 and 2 per cent (Fig. 12). After two weeks of therapy the sedimentation rate dropped from 45 mm./hr. to 12 mm./hr., and thereafter, during therapy, ranged between 12 and 15 mm./hr. (Fig. 13). At the end of one week of therapy with cortisone the chest x-ray (Fig. 14) showed considerable clearing of the multiple large areas of pulmonary infiltration, and at the end of two weeks, almost complete clearing (Fig. 15). Cortisone was given for 36 days ending March 10, 1950. X-ray of the chest on March 16, 1950 (Fig. 16), showed that both lung fields were clear and the cardiac silhouette was smaller.

For the first four days on cortisone there was some fluid retention and on the fifth and sixth days only, an oval, or moon-face was present, but this disappeared on decreased dosage. On the second and fourth days, a slight glycosuria appeared. There has been no glycosuria since. Except for a slight increase of the already existing hirsutism and a mild acne which was present for one week, no other hormonal or other side effects were noted in this patient during the first 35 days of cortisone therapy.

However, on March 10, 1950, the thirty-sixth day of therapy, almost immediately following an injection of cortisone, the patient became markedly dyspneic and cyanotic. The general reaction was severe and the appearance of the patient alarming. In about one minute, the cyanosis completely cleared and the dyspnea subsided. During the reaction the heart rate increased to 160 and examination of the chest revealed a wheezing type of respiration throughout. At this point, cortisone was discontinued. Scratch and intracutaneous tests to the cortisone powder and cortisone powder in saline were negative. An intracutaneous test to cortisone in suspending agents and also to Aqueous Vehicle No. 1 (saline solution containing suspending agents and 1.5 per cent benzol alcohol) gave a moderate reaction. Five control patients tested to Aqueous Vehicle No. 1 showed the following: Three were negative, one, questionable, and the other gave a slight reaction. The effect of cortisone on the chemical constituents of the blood are shown in Table II.

Except for mild wheezing of the chest the patient's general condition continued to improve. However, one week after discontinuing cortisone the cough and wheezing of the chest increased in severity and many moist râles were audible at the right base posteriorly. Because of the possibility of the presence of secondary pulmonary infection, 600,000 units of

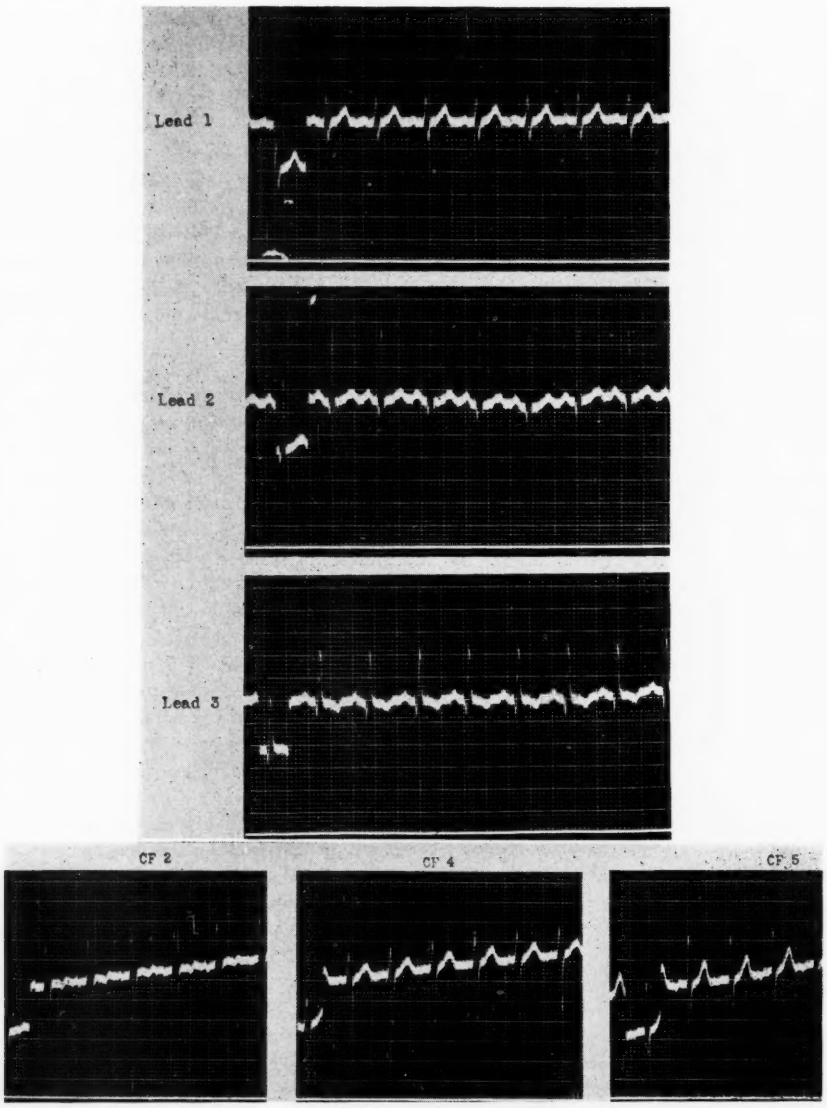

Fig. 8a.—5/6/49. Electrocardiographic tracing showing sinus tachycardia and right axis deviation.

procaine penicillin in aqueous suspension were given daily for 12 days. Subsequent x-ray of the chest on March 29 (Fig. 17), April 11 (Fig. 18), and Aug. 9, 1950 (Fig. 19), showed both lung fields clear and the cardiac shadow remained slightly increased in size. Many subsequent x-rays taken during the following year, the last one on Oct. 18, 1951, also showed both lung fields clear (Fig. 20). The allergic vasomotor rhinitis and bronchial asthma are still present. The temperature and heart rate are normal. The patient's present weight is

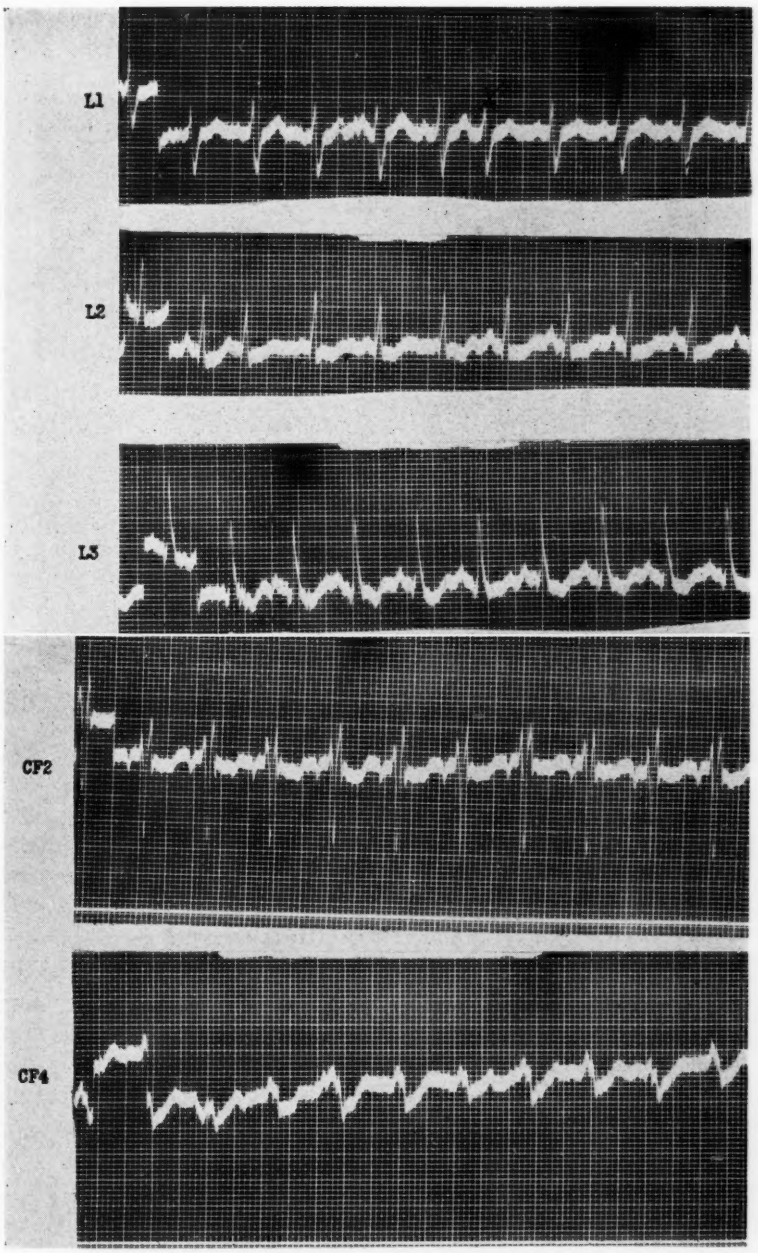

Fig. 8b.—8/14/49. Electrocardiographic tracing showing auricular premature contractions, right ventricular strain and toxic myocarditis.

126 pounds and the anemia, petechiae, arthralgia, polyneuritis, subcutaneous nodules, and albuminuria have disappeared. The cardiac hypertrophy and the right bundle branch block (Fig. 21) are still present. Menstruation occurred on April 2, 1950, after amenorrhea for eighteen months. After discontinuance of cortisone the eosinophil count has ranged between 6 per cent and 20 per cent; the sedimentation rate is still normal.

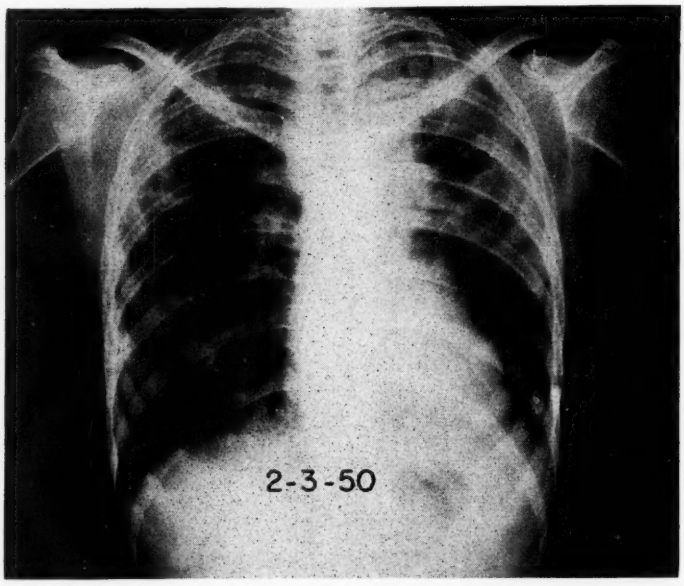

Fig. 9.—2/3/50. Bilateral upper lung field infiltration more marked on left with blunting of costophrenic sinus and displacement of the cardiac shadow to the left. (Before cortisone.)

DISCUSSION

The case presented had an unusual clinical course and review of the literature has not revealed any similar case report. The course was unusually stormy and she showed no response to therapy until cortisone was administered.

Since this patient had primarily and predominently a pulmonary disease characterized by transitory pulmonary infiltrations and an associated eosinophilia, the following diseases were considered in the differential diagnosis: pulmonary tuberculosis, Loeffler's syndrome, Harkavy's syndrome, periarteritis nodosa, coccidioidomycosis, tropical eosinophilia, disseminated lupus erythematosus, amebiasis, ascariasis and other nematodal infections (round, pin, hookworm), Fasciola hepatica, and trichiniasis. Through study of the history, clinical findings and laboratory investigations all could be ruled out in this case except Loeffler's syndrome, Harkavy's syndrome, and periarteritis nodosa.

A comparison between the case presented and those described by Loeffler[2] showed a marked difference in the extent and severity of the clinical course. In Loeffler's series the patients had few and minor symptoms, ran a benign clinical course, had no complications, and no multiple organ involvement. None of Loeffler's cases had asthma. In 14 of 51 patients, the pulmonary lesions were discovered accidentally on routine x-ray examination. Many of them were ambulatory and over 60 per cent were entirely afebrile and the remainder had

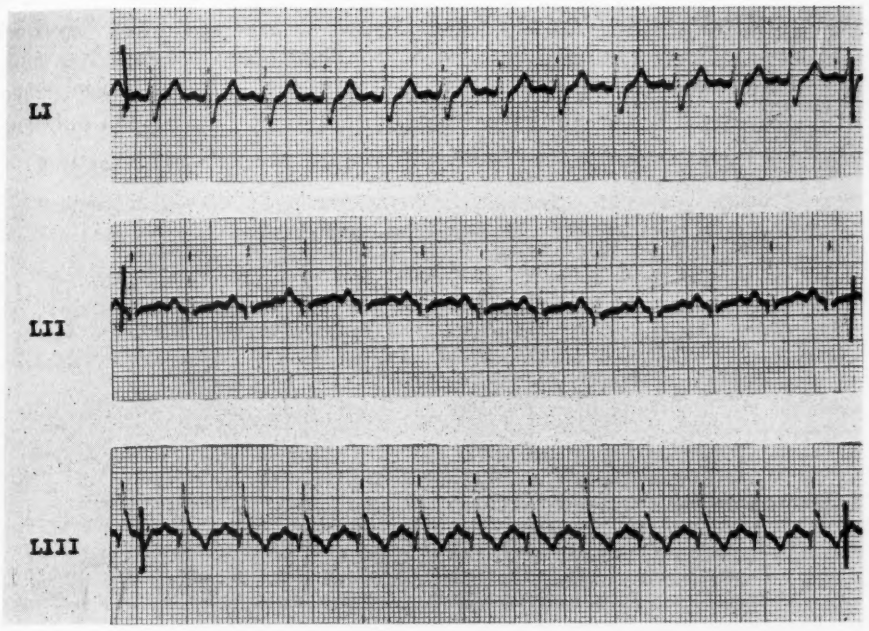

Fig. 10*a*.—2/3/50. Electrocardiographic tracing showing right bundle branch block.

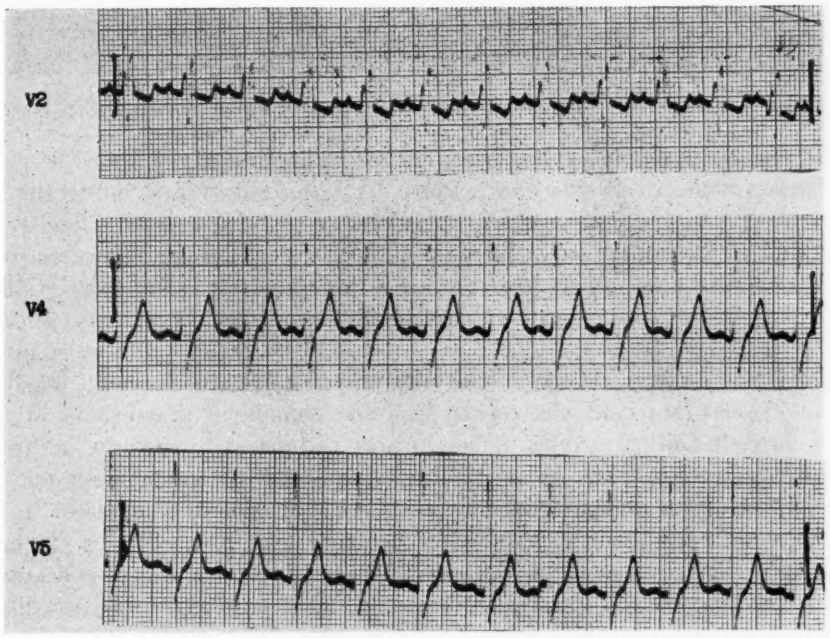

Fig. 10*b*.—2/3/50. Electrocardiographic tracing showing right bundle branch block.

only a slight elevation of temperature. The white blood count was usually normal and occasionally there was a leukocytosis up to 15,000 white blood cells. The sedimentation rate ranged between 8 and 15 mm./hr. and in a few a more rapid rate was observed. The clinical course was very benign and the pulmonary infiltrations cleared in three to eight days. In only one patient, the pulmonary infiltrations reappeared one year after the original episode.

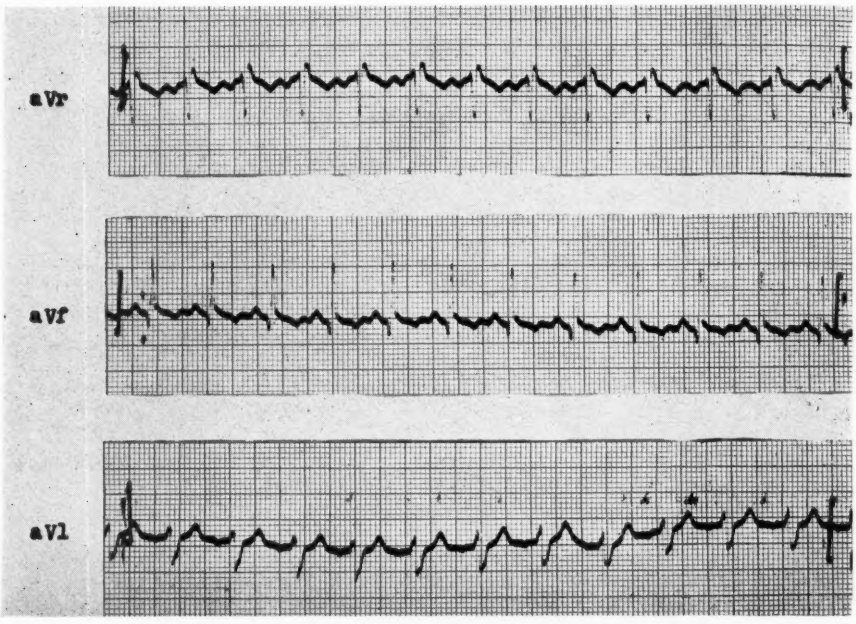

Fig. 10*c*.—2/3/50. Electrocardiographic tracing showing right bundle branch block.

At the onset our patient ran a benign clinical course and fulfilled several of the characteristics of Loeffler's syndrome, i.e.: 1) pulmonary infiltrations, 2) fleeting and changing character of the pulmonary infiltrations, 3) blood eosinophilia, and 4) during the early stages, a mild degree of illness. However, it was soon evident that the patient was running a more prolonged and stormy clinical course than is encountered in a typical Loeffler syndrome. There also appeared multiple organ involvement. There were not only recurrent pulmonary infiltrations of much longer duration, but also myocardial involvement producing cardiac hypertrophy and electrocardiographic changes characteristic of right bundle branch block, purpura, subcutaneous nodules, polyneuritis, arthralgia, albuminuria, and anemia. In addition, this patient had bronchial asthma.

The symptoms and clinical course of this patient were identical in most respects with a group of nine patients reported by Harkavy.[3] In Harkavy's series there occurred bronchial asthma, disease of the sinuses, temperature of 99° to 104° F., recurrent lung infiltrations, pleural effusions, myocardial involvement, mild anemia, leukocytosis, and eosinophilia. In some of his cases the clinical course ran as long as three months. Harkavy's syndrome was characterized by hyperergic responses limited to two or three organs such as the

sinuses, lungs, and heart, and the pathologic processes were reversible. In 8 of the 9 cases there was an arrest in the progress of the disease. There were seven other cases where there was extensive vascular involvement with irreversible changes leading to a fatal issue. Two such cases on necropsy showed periarteritis nodosa.

Although this case resembled Harkavy's syndrome in many respects, it differs in that it is of eighteen months' duration; there is more extensive vascular involvement, and although many reversible changes have occurred, there are still present irreversible responses.

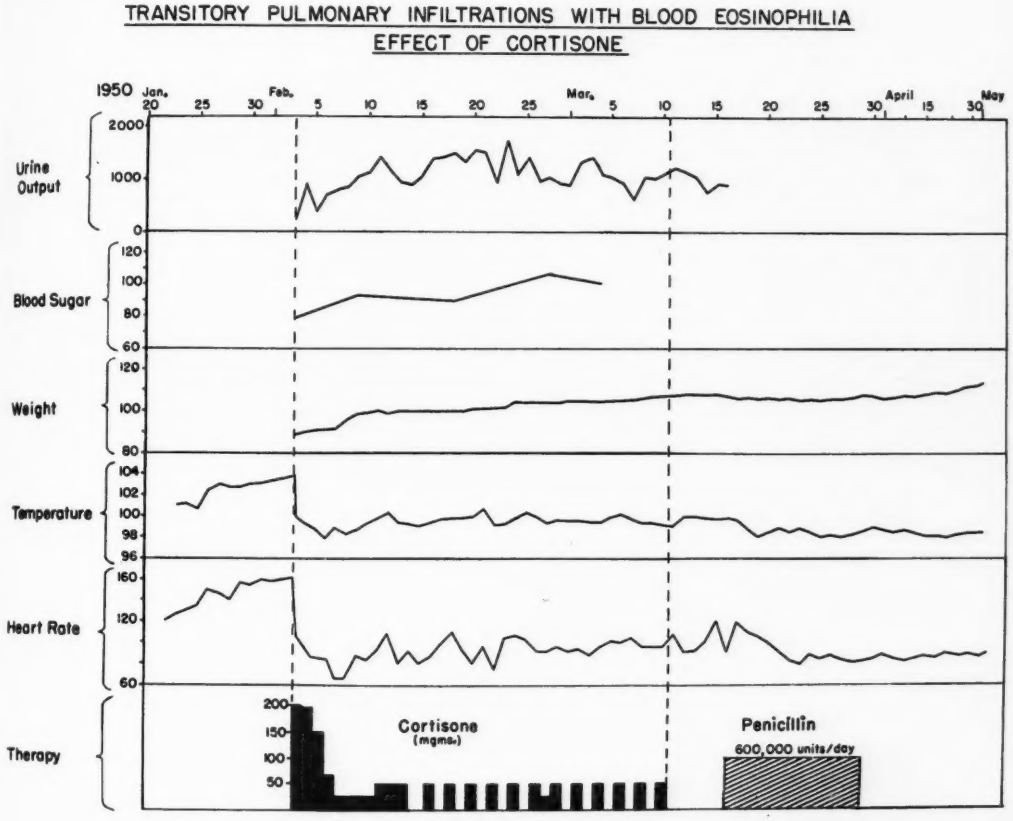

Fig. 11.

The third condition considered in the differential diagnosis was periarteritis nodosa. Solomon, Kasich, and Kiven[4] separated the clinical and laboratory findings into four large groups. First, there are those occurring from the inflammatory process, such as fever, leukocytosis, general malaise, loss of weight, rapid sedimentation rate, anemia, and in general, the picture of fever or sepsis of unknown origin. Second, the symptoms which arise from the involvement of the arteries of particular organs such as the heart, nervous system, gastrointestinal system, or kidneys. Third, allergic manifestations such as eosinophilia

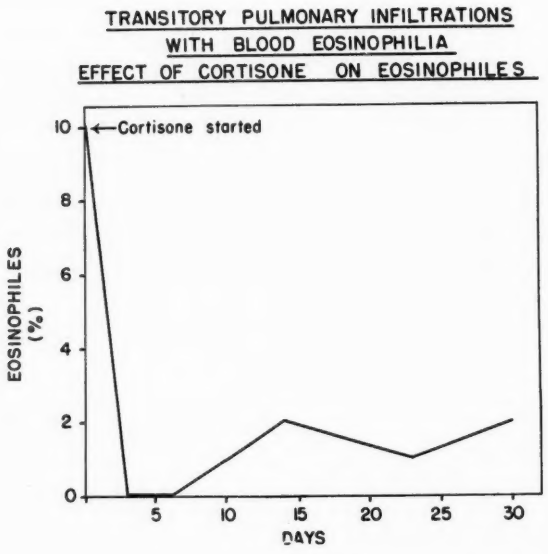

Fig. 12.

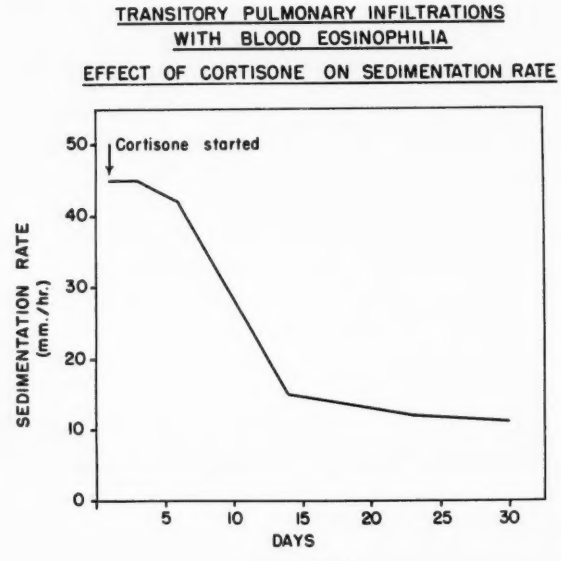

Fig. 13.

Fig. 14.—2/10/50. Almost complete resolution of left lung field changes. Cardiac silhouette still displaced toward the left. (After one week of cortisone.)

Fig. 15.—2/17/50. Cardiac silhouette returning to midline. Old productive changes first and second right interspaces anteriorly. (After two weeks of cortisone.)

Fig. 16.—3/16/50. Cardiac silhouette smaller. Both lung fields clear. (Six days after cortisone was discontinued.)

Fig. 17.—3/29/50. Cardiac silhouette unchanged. Both lung fields clear.

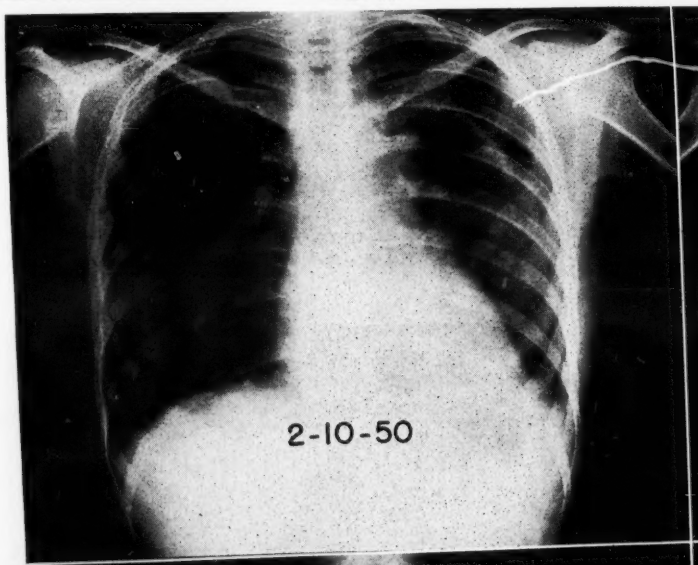

Fig. 16.

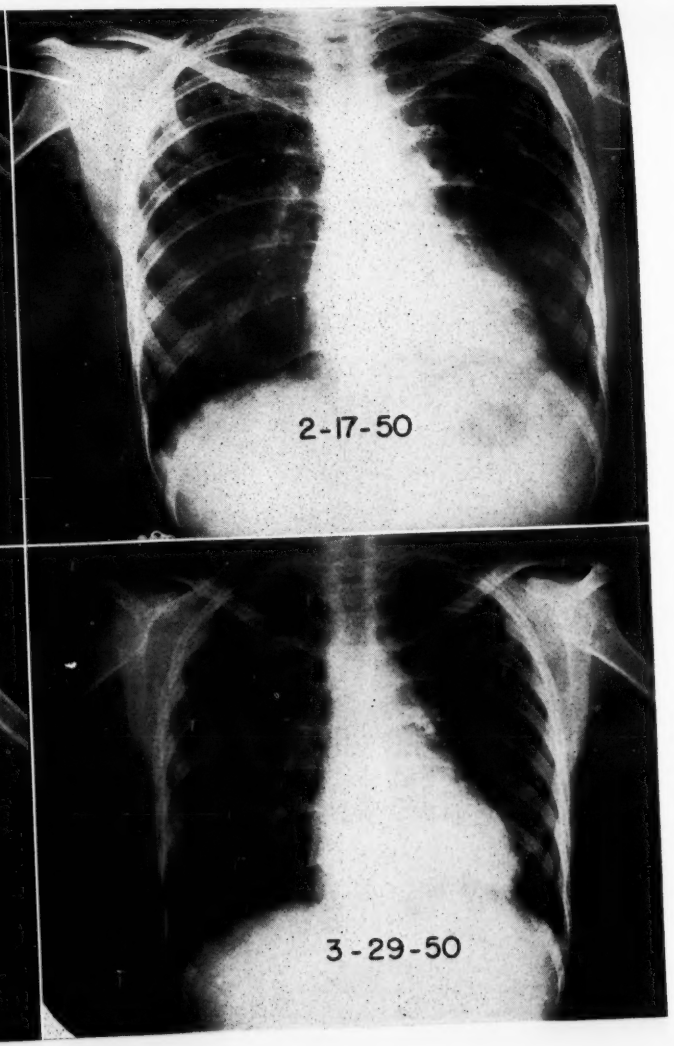

Fig. 17.

(For legends, see opposite page.)

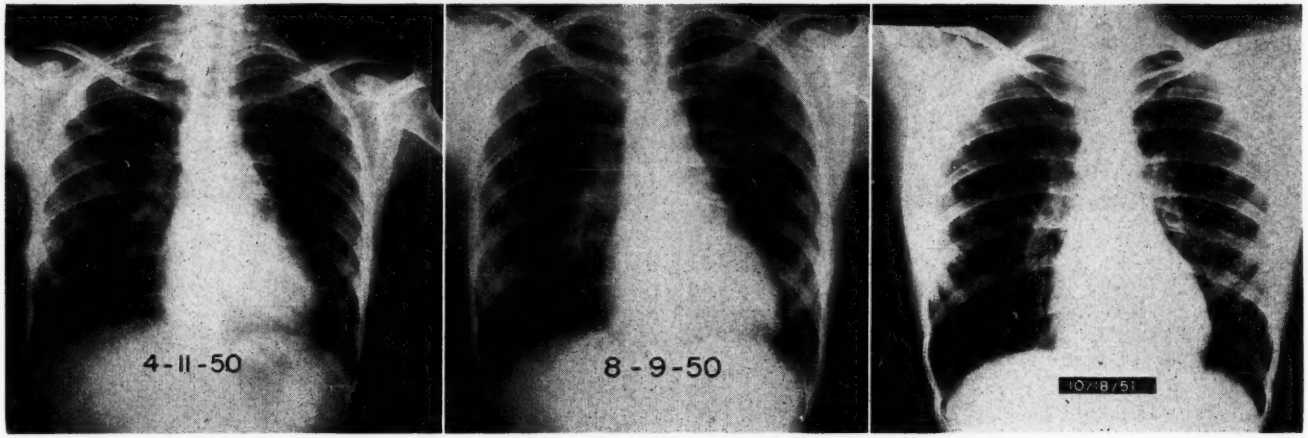

Fig. 18. Fig. 19. Fig. 20.

Fig. 18.—4/11/50. Cardiac silhouette unchanged. Both lung fields clear.
Fig. 19.—8/9/50. Cardiac silhouette still remains slightly increased in size. Both lung fields clear.
Fig. 20.—10/18/51. Both lung fields clear. Cardiac silhouette still remains slightly increased in size.

in the peripheral blood and histologically in the involved arteries and frequently the presence of an associated bronchial asthma; and fourth, palpable arterial nodules and a positive muscle biopsy. It is not necessary for all the above criteria to be present to make a positive diagnosis of periarteritis nodosa. A positive biopsy is conclusive.

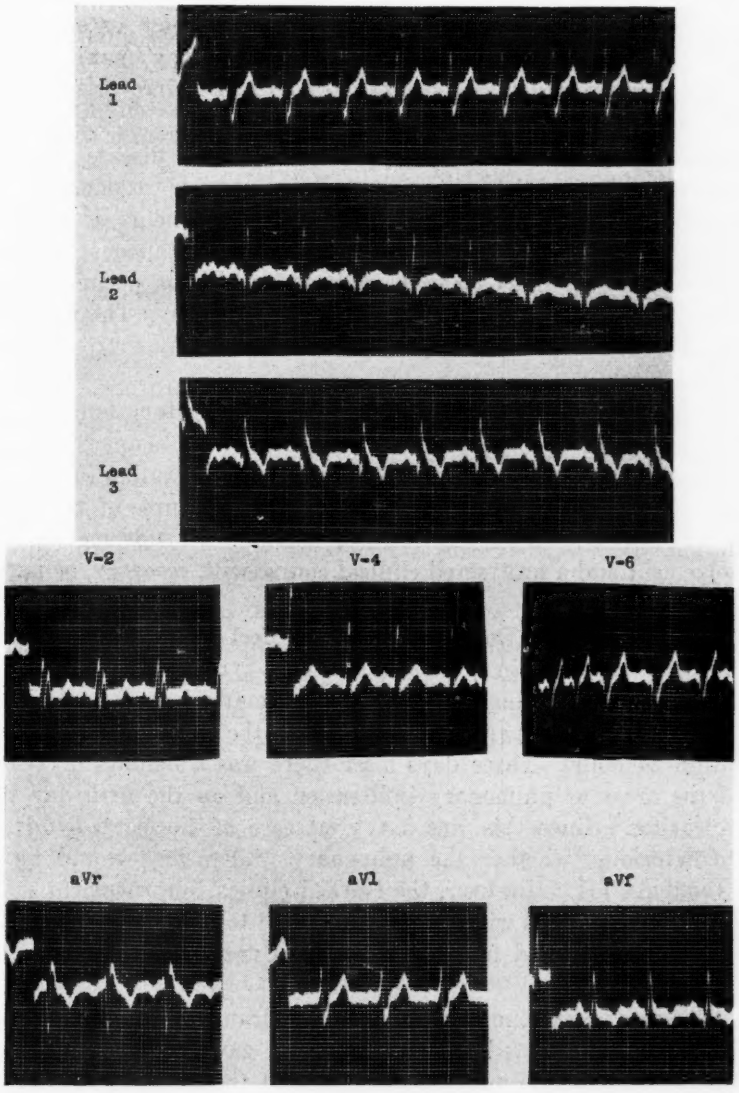

Fig. 21.—Electrocardiographic tracing still showing right bundle branch block.

The case presented was characterized by a clinical picture and laboratory findings resembling those occurring in an inflammatory process, i.e., symptoms arising from involvement of the arteries of the lungs and heart, nervous system, and kidneys; allergic manifestations such as the presence of bronchial asthma

and peripheral blood eosinophilia; and palpable nodules. Biopsy of a muscle and histologic examination of a palpable nodule failed to show evidence of periarteritis nodosa; however, cases have been reported in the literature where repeated biopsies were negative, although at autopsy there was no doubt of the diagnosis. This occurs because of the focal nature of the disease.

Recovery may be complete in periarteritis nodosa with reversible lesions. In these cases the disease was limited and did not show extensive vascular involvement. Certain cases of periarteritis nodosa may manifest reversible reactions at one stage and may develop more extensive irreversible hyperergic vascular disease at some other time.

This case is presented as one of hyperergic vascular disease with extensive involvement characterized by reversible and irreversible responses. On three occasions the pulmonary lesions returned to normal, the heart decreased in size, the polyneuritis and arthralgia subsided, several subcutaneous nodules disappeared, the urinary findings cleared, and the symptoms occurring from the inflammatory process subsided following cortisone therapy. The irreversible responses are characterized by the presence of cardiac hypertrophy and right bundle branch block.

The summary of the history, and clinical and laboratory findings do not as yet fulfill the criteria of any disease entity. The vessel changes in hyperergic vascular disease do not represent disease entities, but rather qualitative and quantitative degrees of allergic response. The future course of the disease will determine whether it is an atypical case of Harkavy's syndrome with multiple organ involvement and a protracted clinical course with recovery, or periarteritis nodosa.

Herbert, DeVries, and Rose[1] reported the effect of pituitary adrenocorticotrophic hormone (ACTH) in a case of Loeffler's syndrome. The most striking change occurred in the eosinophils. There was a marked drop in the eosinophils from 40.4 per cent to 0.5 per cent. Clinically, the patient felt markedly improved within 24 hours. Three days later there was a definite decrease in the density of the areas of pulmonary infiltration and on the fifth day there was complete clearing. Since this was a typical case of Loeffler's syndrome it is difficult to determine whether the pulmonary infiltrations would have disappeared without ACTH. However, the marked clinical improvement in 24 hours and the drop in eosinophils with ACTH suggested to us its use in this case after other forms of therapy had failed. ACTH was not available at that time but cortisone was.

Two courses of cortisone were given with dramatic results. It is not believed that cortisone affected a "cure" but it gave the patient tremendous benefit and interrupted the unfavorable course of the disease. Within 24 hours there was a feeling of remarkable improvement. There was no true euphoria, but the patient expressed a sense of well being and improved morale. This continued even after cortisone therapy was stopped. The hematologic response was characterized by a drop in eosinophils from 10 per cent to 0 in 72 hours and it ranged between 0 and 2 per cent during 35 days of cortisone therapy. After two weeks of medication the sedimentation rate dropped from 44 mm./hr. to

14 mm./hr. The areas of pulmonary infiltration had almost completely disappeared at the end of two weeks' treatment. Subsequent x-rays showed complete clearing with no recurrences of the areas of pulmonary infiltration. X-ray of the chest on Oct. 18, 1951, nineteen months after cortisone was discontinued, also showed both lungs normal.

SUMMARY AND CONCLUSIONS

1. A case of transitory pulmonary infiltrations with blood eosinophilia is reported.

2. The patient had an unusually stormy and protracted clinical course of eighteen months' duration.

3. Clinically it was characterized by allergic rhinitis, bronchial asthma, fever, tachycardia, fatigue, transitory pulmonary infiltrations, blood eosinophilia, loss of weight, anemia, purpura, arthralgia, polyneuritis, subcutaneous nodules, albuminuria, cardiac hypertrophy, and right bundle branch block.

4. Biopsy of muscle tissue and a subcutaneous nodule did not reveal evidence characteristic of any recognized disease syndrome.

5. At the present time the case is presented as one of hyperergic disease with extensive multiple organ involvement characterized by reversible and irreversible responses, which in many respects resembles Harkavy's syndrome.

6. Administration of cortisone produced remarkable clinical improvement. It caused a disappearance of the clinical symptoms occurring from the inflamatory process, such as fever, leukocytosis, general malaise, loss of weight, and rapid sedimentation. It also produced a disappearance of the pulmonary infiltrations, anemia, purpura, arthralgia, polyneuritis, albuminuria, and subcutaneous nodules. During the course of cortisone there was a marked decrease in the eosinophil count, only to become increased again on the discontinuance of cortisone. Cortisone had no effect on the right bundle branch block and cardiac hypertrophy. It is believed that cortisone interrupted the unfavorable course of the disease and induced very marked clinical improvement.

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STUDIES IN ATOPIC DERMATITIS. IV. IMPORTANCE OF SEASONAL INHALANT ALLERGENS, ESPECIALLY RAGWEED

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IN OUR previous publications,[1-4] which included a complete review of the literature on this subject as well as reports of our own studies, we emphasized the importance of inhalant allergens in the causation of atopic dermatitis. We also established the fact that the specific lesions of the disease could be induced by the inhalation of house dust and alternaria in a susceptible subject. These studies served to verify more definitely previous assumptions based purely upon clinical evidence that inhalant allergens were important etiologic factors in atopic dermatitis and stressed the necessity for their greater consideration in its treatment.

In our first report in 1949[1] a high incidence of positive skin test reactions to pollens, especially ragweed, was noted—thus of the 54 patients studied, only 5 had completely negative reactions to ragweed pollen extract whereas 49 had positive skin test reactions, 32 in moderate or marked degree. Twenty-two of the 49 positive reactors had a clinical history of seasonal hay fever and/or asthma to substantiate the positive skin test reaction. It seemed to us at that time that such a high incidence of positive reactors must be more than mere coincidence. It suggested the possibility that pollen allergy perhaps was a more important etiologic factor in atopic dermatitis than we had previously suspected, a fact which was worthy of further investigation. The present report concerns itself with subsequent studies designed to determine the role which seasonal inhalant allergens, and in particular ragweed pollen, play in atopic dermatitis.

That ragweed might be important is not new. Others in the past have called attention to this. Thus, for example, Cazort in 1936,[5] in a paper concerned with the importance of the house dust antigen in allergy, cited five cases of "neurodermatitis" in which dust was the most important factor. In one of the five, there was a flare-up of the dermatitis during the oak pollen season while the patient was also having hay fever from the oak pollen. No attempt was made, however, to elaborate on the possible etiologic relationship of the oak pollen in that particular patient. Further suggestion of an etiologic relationship was made shortly thereafterward by Rowe in 1937[6] and by Feinberg in 1939,[7] both of whom showed in clinical reports that pollen as well as molds apparently were responsible for seasonal aggravation of atopic dermatitis. In 1946 Rowe[8] again reported the occurrence of dermatitis of the hands as the major or sole manifestation of inhalant pollen allergy in 22 patients.

But despite these reports, little attention apparently has been paid to seasonal inhalants, especially to ragweed pollen, as important inhalant etiologic factors in atopic dermatitis. Furthermore, the evidence to prove this relationship has been purely clinical with no attempts being made to definitely establish

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pollen as a direct cause in a manner, for example, like that previously accomplished by us with house dust and alternaria. It seemed worth while, therefore, for us to try to obtain this evidence by further investigation, the results of which constitute the basis for the present report.

In proceeding with our studies, we first tried to find out whether our original estimates of the high incidence of positive pollen reactors were correct by studying a larger group (136) of patients with atopic dermatitis. Most of these were seen in private practice but we have also included a small number of patients (13 or 9.5 per cent) who were studied by us in the outpatient clinic of Temple University Hospital. Of the 136, 64 were adults and 68 children up to the age of 12, inclusive. Four were infants under the age of 1.

All these patients were tested by the intracutaneous method in the same manner and with the same extracts as we used in patients with asthma or seasonal hay fever. Since our pollen extracts are standardized by the total N method, most of the patients were tested with concentrations varying from .0001 to .1 N. In most instances, the recorded results of the skin test reaction represent the .1 mg. N concentration, unless a marked reaction was obtained in the .001 or .01 dilution, precluding the necessity for testing with the .1 N strength.

TABLE I. SKIN TEST RESULTS IN PATIENTS WITH ATOPIC DERMATITIS

ALLERGEN TESTED		SKIN TEST REACTIONS				NO. TESTED	NO. POS.	PER CENT POS.
		NEG.	SL.	MOD.	MKD.			
Ragweed	.1	15	42	41	38	136	121	88.9
Timothy	.1	64	54	10	7	135	71	52.6
English Plantain	.1	69	53	7	5	134	65	48.5
Alternaria	1-10	50	20	18	7	95	45	47.4

The results of these studies are summarized in Table I and the close similarity to the findings in our first report is immediately evident. Here again, the incidence of positive reactions to ragweed is noticeably high (88.9 per cent) in comparison to the other pollens; and of the 136, 79 or 58 per cent were of moderate to marked degree. Proportionately fewer positives were obtained with timothy and English plantain. It is interesting that this proportion corresponds roughly to the incidence of positive pollen reactions seen in hay fever patients in our area. To complete the incidence for seasonal inhalant allergens, we have included in Table I the positive reactions to alternaria which is the predominant atmospheric mold in this area. Here, too, a fairly high incidence was obtained although only 25.9 per cent were of moderate or marked degree.

These findings done on a larger group of patients again confirm the fact that atopic dermatitis patients seem to have a rather high incidence of positive reactions to seasonal inhalant allergens, notably ragweed pollen. One immediately might ask whether this also would be true of other allergy patients who do not have either atopic dermatitis or an allergic condition in which seasonal inhalant allergens are unlikely to be operative. Therefore, in order to provide a control group, we next reviewed the record of 100 consecutive patients with allergic conditions in which pollen was not likely to be a factor

(e.g., patients with urticaria, angioedema, migraine and other headaches, contact dermatitis, gastrointestinal conditions in which allergy was suspected, etc.) and in whom in the course of routine skin testing, tests to pollens also had been included.

The results of these studies are summarized in Table II. This shows strikingly that the incidence of positive pollen reactions was quite low compared to that in patients with atopic dermatitis. Thus only 5 per cent gave positive reactions to ragweed and all these were of slight degree. This low incidence certainly stands in definite contrast to the almost 90 per cent incidence in the atopic dermatitis group. It proves convincingly that the high incidence of reactions to seasonal inhalant allergens in atopic dermatitis patients was not a normal reaction and certainly could not be a matter of accident or coincidence.

TABLE II. SKIN TEST RESULTS IN CONTROL GROUP

ALLERGEN TESTED	SKIN TEST REACTIONS		NUMBER TESTED	PER CENT POSITIVE
	NEGATIVE	SLIGHT		
Ragweed .1	95	5	100	5
Timothy .1	91	9	100	9
English Plantain .1	93	7	100	7
Alternaria 1-10	30	3	33	9.9

How, then, could one satisfactorily explain this high incidence, especially to ragweed pollen? Three possibilities suggested themselves: (1) that the positive skin test reaction to ragweed (and for purposes of simplicity, we will refer in all subsequent discussions only to this pollen, rather than to all the seasonal inhalants) was unrelated etiologically to the dermatitis and, therefore, independent of its production. This would be true if the reaction could be explained by an associated seasonal hay fever and/or asthma, either present at the time the patient was seen or appearing some time in the future. In the latter instance, the skin sensitization to ragweed would represent the earliest indication in that patient of the future clinical development of hay fever; (2) that the positive reaction was related etiologically to the dermatitis and was responsible both for the hay fever and for the seasonal outbreaks of dermatitis; or finally, (3) that the ragweed reaction was related etiologically, being responsible solely for the dermatitis and no other clinical manifestation. This would be verified either by seasonal outbreaks of dermatitis either alone or in patients with perennial atopic dermatitis.

In order to provide evidence for these situations, we next reviewed the histories of the 121 atopic dermatitis patients who had positive ragweed reactions to determine in what proportion there was a history of associated seasonal hay fever and/or asthma.

As seen in Table III, this was true in 64 or 52.8 per cent of the 121 patients. Of the 64, 13 had seasonal outbreaks of atopic dermatitis which occurred only during the ragweed hay fever season along with the usual nasal symptoms. In 12 of the 13, the dermatitis was quite mild but in the thirteenth, a man of 35, it was unusually severe and for three seasons almost completely replaced the hay fever symptoms which had been present for more than

TABLE III. ANALYSIS OF 121 POSITIVE RAGWEED REACTORS OUT OF A TOTAL OF 136 ATOPIC DERMATITIS PATIENTS

NATURE OF DERMATITIS	ASSOCIATED RAGWEED HAY FEVER AND/OR ASTHMA	NO ASSOCIATED HAY FEVER
Seasonal	13	3
Perennial with seasonal aggravation	23	20
Perennial with *no* seasonal aggravation	28	34
Total No.	64	57

twenty years. This is an exceptional occurrence for in the other 12 patients the dermatitis was so mild that it easily could have been overlooked or have been regarded as outbreaks of prickly heat, as was true in some of these patients. However, in the latter instances, the flexural distribution and character of the lesions as well as a history of similar more intense eczematous outbreaks in infancy or early childhood plus their recurrence during the hay fever seasons enabled us to establish the diagnosis, as in the following illustrative case reports.

CASE REPORTS

CASE 1.—D. G., a 45-year-old man, was first seen Oct., 1948, with a history of fall hay fever and asthma of many years' duration. He also stated that he developed mild itching dermatitis involving the backs of the legs and apparently appearing only during the hay fever season. The dermatitis was not evident at the time the patient was seen but reappeared in Sept., 1949, despite pollen therapy. In April, 1950, mild itching of the affected leg area followed the injection of a small dose of ragweed-mold extract (.0002 N) necessitating reduced dosage. The itching disappeared shortly thereafter and except for slight recurrence during August, 1950, he experienced no further difficulty. During the 1951 hay fever season he had neither itching nor eruption.

CASE 2.—C. H., a 35-year-old man, was first seen in 1938 complaining of hay fever and asthma. Detailed questioning revealed that he had a mild itching type of dermatitis in the flexures during the ragweed hay fever season but had disregarded them.

CASE 3.—C. W., a 6-year-old girl, was first seen the end of September of 1948 because of seasonal hay fever and perennial allergic rhinitis of 3 years' duration. She had eczema during infancy but this disappeared during her second year of life. Pollen therapy was begun on 4/26/49. On 6/6/49 the patient developed an itching, papular eruption in the antecubital, thigh, and chest regions after the injection of ragweed pollen extract (.0006 N) necessitating reduction in dosage. The eruption disappeared but recurred in mid-September in the antecubital, thigh, and popliteal areas, persisting for about 2 months before disappearing. At that time, the mother recalled that at about the same time during the previous hay fever season (1948), before the child had received treatment, a similar eruption had occurred but was milder and of shorter duration. There was no further recurrence of the eruption either during 1950 or 1951, while under pollen therapy, and only mild hay fever symptoms were experienced.

These case reports illustrate how it is possible to overlook mild seasonal outbreaks of atopic dermatitis in patients with seasonal hay fever unless one is watching for it. In such instances, however, it is clear that both the hay fever and the dermatitis are provoked by the allergic reaction to ragweed pollen and account for the positive skin test reaction.

Twenty-three other patients of the 64 with associated hay fever had perennial atopic dermatitis from various causes (food and inhalant), but the

dermatitis noticeably increased during the ragweed hay fever season. This is well illustrated in the following case report.

CASE 4.—C. G., a 21-year-old woman, was first seen in October, 1946, because of early hay fever present since the age of 9 and of fall hay fever of 2 years' duration complicated by asthma beginning in 1945 and persisting throughout the winter and subsequent spring. She had flexural eczema in infancy which persisted throughout her childhood and was worse in the summer with mild recurrences thereafter. In August, 1946, she developed dermatitis of the fingers of both hands which persisted until she consulted us. At that time she had a mild antecubital outbreak which seemed to be more evident after scratching. Many positive intracutaneous skin test reactions were obtained to such inhalants as dust, feathers, wool, animal danders, timothy, English plantain, ragweed, some local trees, and to many foods, some of which could be verified by clinical diet trial. Thus, for example, ingestion of such foods as chocolate or tomato caused increased itching of the erupted areas. Although the eruption persisted in mild degree on the hands throughout the winter, there was definite aggravation during August and September of 1947 and 1948. This likewise was true in 1949, but at that time the patient went for a short vacation to the White Mountains where there is relatively little or no ragweed pollen in the atmosphere. While there, the dermatitis of the hands cleared up, only to recur upon her return home during the height of our local ragweed season.

This case report illustrates well the type of patient who has perennial atopic dermatitis and associated hay fever and asthma, in whom aggravation of the dermatitis is provoked by sensitivity to ragweed pollen. The involvement of the hands in this patient is similar to the cases reported by Rowe[8] in 1946. Similar involvement of the fingers of the hand was not frequent in our experience, having been present in none of the 13 with strictly seasonal outbreaks, and in only 3 of the 23 patients in the group with seasonal aggravation of perennial dermatitis along with hay fever. In most of these patients, the flexures were chiefly involved.

Adding together the 13 strictly seasonal cases and the 23 with seasonal aggravation of perennial dermatitis, it means that in 36 of the 64 patients with associated hay fever, the positive ragweed reaction could be accounted for upon the basis that it was the cause of both the hay fever and the dermatitis. This leaves for consideration the remaining 28 patients with both hay fever and atopic dermatitis in whom no seasonal outbreaks were noted. Here the positive ragweed reaction can be explained upon the basis of their associated hay fever, the dermatitis in such instances being provoked by other allergenic agents. This is well illustrated in the following case reports.

CASE 5.—J. A., a 42-year-old man, was first seen 3/15/46 because of fall hay fever and asthma of many years duration. Skin tests were done at that time to pollens and inhalants only and were positive to ragweed, timothy, English plantain and sycamore and to house dust, and other inhalants. Preseasonal treatment with ragweed pollen and dust extracts during 1946 and in subsequent seasons was followed by good results, the patient experiencing only very mild hay fever symptoms. In March, 1947, when the patient returned to begin his preseasonal treatment, he had mild dermatitis of the face and ears of several months' duration for which he was being treated by a dermatologist. By February, 1948, this had spread to the extremities and was quite severe. A diagnosis of nummular eczema had been made by several dermatologists and despite intensive local treatment, the condition grew progressively worse. The patient, being quite discouraged then, did nothing further and the condition persisted. It got worse during the hay fever season in 1948, improved in the winter 1948 to

1949 but became worse again in the spring of 1949. At that time, the patient finally, and as a last resort, consented to being tested to foods and showed many positives, especially to pork, green pea, chocolate, tomato, orange, and spinach. Elimination of these foods, especially pork and chocolate, was followed by striking improvement which continued as long as the patient adhered to the diet. Clinical trial showed definite aggravation after the ingestion of pork, orange, tomato, and chocolate.

CASE 6.—E. J. M., a 62-year-old man, admitted to Temple University Hospital March 11, 1938, was referred for allergic study because of extensive generalized atopic dermatitis, so diagnosed by the dermatologist and present since November, 1937. His condition cleared for a while in January while the patient was away from his home in Wilkes-Barre, but recurred within 10 days after returning home, becoming increasingly severe and extensive. The patient had fall hay fever for ten years, not improved by pollen therapy. Because of the extensive skin involvement, tests were done by passive transfer. Reactions were found in marked degree to house dust, ragweed, timothy and, to a lesser extent, to some food allergens. His condition cleared up remarkably while in the hospital and subsequently in Atlantic City so that in almost a month it became normal in texture and appearance. Dust was obtained from the patient's home and an extract prepared to which he gave both a marked skin reaction and a positive passive transfer reaction. He was instructed to return to Wilkes-Barre but not go to his own home for several weeks until the house could be rid of dust-containing articles and until some desensitizing injections of the dust extract had been given. He finally returned to his home without difficulty. The injections were discontinued after about two years, and, when recently seen, the patient reported that there had been no recurrence for a period of more than 8 years.

In both these illustrative case reports, the dermatitis was provoked by nonpollen allergens—foods in Case 5, and house dust in Case 6. But both patients had an associated hay fever which was completely unrelated to their dermatitis and which was responsible for their positive ragweed reactions. This also was true of the other patients making up the group of 28 with perennial atopic dermatitis and unrelated hay fever.

So much then for the 64 patients with associated hay fever in whom the positive ragweed reaction is easily accounted for either as producing the hay fever alone or both the hay fever and the dermatitis. What about the positive reactions in the other 57 who had no history of associated hay fever? In three patients in this group, the dermatitis was strictly seasonal as indicated in the following case report.

CASE 7.—A. B., a 26-year-old woman, was first seen 10/13/50 because of perennial allergic rhinitis and mild asthma of several years duration. She also had a mild scaly, itching eruption involving the skin of both upper eyelids, antecubitals, and right thigh. This had been present since August, 1949, persisting until November, 1949, and recurring again in August and September, 1950. Intracutaneous skin tests were positive to ragweed, timothy, hickory, dust, feathers, orris, wool, and several foods. In March, 1951, on 2 occasions she had increased itching of the eyelids after injections of ragweed pollen extract (.005 N) necessitating reduced dosage. On 8/24/51 after the skin had been relatively clear, the patient noted an eruption of the eyelids, face, and fingers lasting a week. This was less intense than in previous seasons.

All three patients had associated perennial allergies of a respiratory character and provoked by other nonpollen allergens. But all of them had seasonal outbreaks of dermatitis during the ragweed hay fever season to account for the positive ragweed reaction, since none of them had as yet an associated seasonal hay fever.

Twenty other patients in this group had a perennial atopic dermatitis from various causes which became aggravated during the ragweed season. Most of these were patients who had consulted us primarily either because of the dermatitis or because of perennial rhinitis or asthma. But after continued close observation, it was found that the dermatitis worsened during the ragweed season, thus accounting for their positive skin test reaction to ragweed.

In the remaining 34 patinets with perennial dermatitis and no apparent associated hay fever, the positive ragweed reaction could not be attributed either to the dermatitis (as indicated by a seasonal aggravation) or to an associated ragweed hay fever. Five patients in this group did not return after the completion of their diagnostic studies and were therefore not followed long enough to determine the possible clinical importance of the positive ragweed reaction. But in the remaining 29, the dermatitis improved after the institution of food or inhalant elimination, so that the positive ragweed reaction still was unaccounted for. It is entirely possible, of course, that in these 34 patients and in the 20 with seasonal aggravation of dermatitis, the positive ragweed reaction may represent the first evidence of the future development of hay fever in that patient, the skin having been the first tissue to be sensitized (a future clinical positive). This supposition is enhanced first by the fact that many of these patients had strong atopic family histories especially of hay fever and second by the fact that a few of them, as shown by subsequent observation, developed hay fever. This is illustrated in the following case reports:

CASE 8.—C. D., a 3-year-old girl, was first seen in April, 1947, with flexural atopic dermatitis involving the antecubitals, wrists, and popliteals and present constantly since the age of 18 months with no apparent seasonal aggravation. Intracutaneous skin tests were positive to such inhalants as house dust, feathers, orris root, and wool and to several foods. Despite the absence of any clinical hay fever, the patient had a positive skin test reaction to ragweed in slight degree. Following the elimination of the test-positive foods and avoidance of the offending inhalants (notably wool) the eruption disappeared so that specific desensitization was considered unnecessary. In September, 1951, the patient developed typical symptoms of ragweed hay fever associated with mild wheezing which responded to routine symptomatic treatment.

CASE 9.—V. S., a 2-year-old girl, was first seen 12/11/46 with persistent atopic dermatitis involving cheeks, back of the neck, and flexures, present since early infancy and unresponsive to various treatments. Both the attending pediatrician and dermatologist advised local treatment only, thinking she "would grow out of it." Family history was strongly atopic. Intracutaneous skin tests were positive to dust, wool, milk, and a few other foods and to ragweed pollen. Improvement followed the elimination of milk and avoidance of dust and wool contact; also after residence at the seashore, although patient had some recurrence upon her return home from the seashore, particularly in August and September, both in 1947 and 1948. The patient had no clinical symptoms of hay fever during this period but in early September, 1949, while in Beach Haven, N. J., she developed mild hay fever symptoms for the first time. This was accompanied by a mild outbreak of the dermatitis which persisted for several months.

Both these case reports are examples of patients in whom the positive reaction to ragweed pollen antedated the onset of clinical hay fever symptoms; in the first case by about 4 years and in the second by 3 years. Naturally if such patients are seen at the time they have the dermatitis without evidence

of clinical hay fever, the positive pollen reaction may represent either a future or potential pollen reactor which as in the first case (No. 8) had no etiologic relationship to the dermatitis or as in the second case (No. 9) was related both to the dermatitis and the hay fever.

As already indicated it was not possible for us to determine how many of the patients with unexplained positive ragweed reactions were of the future clinical positive type. But since many of these patients were children or very young adults and came of atopic families often with histories of hay fever, this possibility does not seem unlikely.

From the evidence thus far presented, therefore, it seems quite clear, at least from a clinical standpoint, that a positive skin test reaction to ragweed pollen, obtained in patients with atopic dermatitis, sometimes may bear no etiological relationship whatsoever to the dermatitis, but is the result of an associated hay fever, present at the time the patient is seen or appearing some time in the future. The dermatitis in such patients is due to other nonpollen factors. But in other patients, the pollen sensitivity is definitely related etiologically to the dermatitis. Proof of this already has been provided clinically in 59 patients of whom 36 had associated hay fever and seasonal outbreaks of atopic dermatitis. The remaining 20 patients had perennial dermatitis from various nonpollen causes, but developed seasonal aggravation of the dermatitis because of their allergy to ragweed pollen.

The clinical evidence provided by the above analysis of our case histories should suffice to strongly favor the probable etiologic importance of pollen especially ragweed as an inhalant allergen in atopic dermatitis. But to make it even more convincing, we now tried to obtain supportive experimental evidence. We utilized for the latter purpose those methods previously employed by us in establishing the etiologic significance of house dust and alternaria as inhalant allergens; that is, by inducing the dermatitis either (a) by repeated inhalation of ragweed pollen or (b) by the injection of ragweed extract into susceptible subjects.

Our attempts to induce the dermatitis by deliberate repeated inhalation of ragweed pollen through the nose was hampered greatly by the fact that sneezing or asthma were induced in those patients who had associated hay fever or asthma and thus the pollen was prevented from getting into the blood stream. Consequently, we were able to carry out this procedure with some degree of success in only two patients, both of whom had atopic dermatitis with no associated clinical hay fever. In both instances, a single instillation of dry ragweed pollen into the nose was followed within a short time by mild outbreaks of the affected skin areas, as indicated in the following case reports.

CASE 10.—M. F., a 28-year-old man, was first seen 9/18/51, having been hospitalized at Temple University Hospital because of atopic dermatitis involving the face, neck, flexures, and ankles since June, 1951. Two sisters had eczema, one with associated hay fever, and his mother had migraine. The patient apparently had no known associated allergies, especially hay fever and/or asthma. Positive skin test reactions were obtained to ragweed, alternaria, house dust, wool, feathers, dog epithelium, and several foods. Two weeks after the institution

of allergy treatment (elimination of offending allergens and diet trial) the skin condition improved greatly. On the morning of 10/3/51, when the skin was relatively clear, a nasal test with dry ragweed pollen was done. Immediately after its inhalation into the nasal cavity, the patient noted slight rhinorrhea followed shortly by some itching in the affected skin areas. In the afternoon of the same day, the skin of the face began to break out, especially around the mouth and upon the cheeks and chin. These areas were red, dry, and blotchy. This eruption lasted about three days, gradually fading away.

CASE 11.—B. A., a 31-year-old man, was first seen 9/29/49 with moderately severe atopic dermatitis since infancy. The eruption affected the antecubital and popliteal fossae, face, neck, and thighs. It had persisted almost without change, despite all the usual forms of dermatologic treatment, except for a period of four months in 1942 while in an army hospital. Upon close questioning, it was revealed that he had an increase in his dermatitis on or about September 4, 1949, as well as in the fall of 1947 and 1948 but the 1949 increase was considered the worst of the three. He also had mild associated sneezing and rhinorrhea present for about a year but apparently worse coincident with the dermatitis. This clinical evidence of possible ragweed sensitivity was supported by a positive skin test reaction to ragweed pollen, in addition to positives to other inhalants and foods. Hospitalization of the patient at Temple University Hospital was followed within a short period by marked improvement in the dermatitis. In order to determine the effect of the ragweed pollen, a nasal test was done. Sufficient dry ragweed pollen to cover the flat end of a toothpick was inhaled. There was immediate sneezing and rhinorrhea, followed in a short time by itching and sweating in the antecubital and popliteal fossae and later by a mild outbreak of the dermatitis which persisted for several days.

The dermatitis induced in both these patients though mild in character was the same in all respects to that which the patients previously had. And since both patients formerly were treated by competent dermatologists for atopic dermatitis, one necessarily must conclude that the lesions so induced by the inhalation, likewise, were those of true atopic dermatitis. In both patients, the induced dermatitis was of short duration, its disappearance having been aided perhaps by the intramuscular administration of Benadryl. If these patients could have inhaled the ragweed pollen daily as they do during the hay fever season, we might have induced a more severe type of dermatitis at regular intervals as we were able to do with house dust and alternaria in the patient reported in previous studies.[2, 3] This was not feasible, however, in these two patients who were discouraged even by this mild outbreak which they attributed to our test. Nevertheless, we feel that the reproduction of the dermatitis, even though mild, following the inhalation of the ragweed pollen can be considered as evidence of its etiologic relationship. This is substantiated to some extent by the fact that of the many hundreds of nasal tests performed by us upon patients with uncomplicated hay fever in which similar amounts of ragweed pollen were inhaled into the nasal cavity, to our knowledge dermatitis never was so induced. This suggests that the inhalation of ragweed pollen will induce dermatitis only in those patients so predisposed.

The induction of dermatitis by the injection of ragweed pollen extract proved to be a much easier experimental method. In some instances this was unintentional or accidental, that is, the dermatitis followed the injection of the extract given for purposes of desensitization. This was in reality a constitutional reaction, much like the asthma which follows vaccine overdosage in asthmatics or of the hay fever and urticaria after pollen overdosage in uncom-

plicated hay fever patients. This occurred in 16 of those patients treated with ragweed pollen extract. In some it happened only once, but in others, it followed the injection several times in the same patient, as for example, in case reports Nos. 1, 3, and 7. Whenever possible, we tried to determine whether the dermatitis resulted from the injection. That it was specific was indicated by the fact that it did not follow the injection of buffered saline solution used as a control; also that it could be induced repeatedly in the same patient by the injection of ragweed pollen extract.

But in order to obtain more definite proof, we next tried to induce the dermatitis intentionally by the deliberate injection of a more concentrated ragweed extract into susceptible subjects. This could be carried out only in 2 patients but with the following results.

CASE 12.—M. P., a 27-year-old woman, had flexural atopic dermatitis since childhood as well as an associated allergic rhinitis and fall hay fever. When her skin had become practically clear, she was injected with 0.1 c.c. of a concentrated ragweed extract (0.6 N) intracutaneously. This was followed shortly thereafter by a marked increase in the eruption. Later, when skin had again cleared, the same procedure was repeated. The injection again was followed by a popliteal eruption beginning within 12 hours after the injection.

CASE 13.—D. F., a 23-year-old woman, was first seen in May, 1950, with atopic dermatitis since 6 months of age and associated asthma of more recent origin. On 9/28/50, when her skin was clear, she was given 0.1 c.c. of a ragweed pollen extract (0.01 N) intracutaneously. This was followed by immediate marked sneezing which persisted for the following two days. Upon the third day after injection, she developed a moderately severe eruption in her antecubital fossae, wrists, and neck, which cleared within a week under appropriate treatment. On 10/12/50, when her eruption had practically disappeared, she was again injected intracutaneously with 0.1 c.c. of a more concentrated ragweed extract (0.4 N). Within a short time the patient began to sneeze, cough and wheeze. This was followed by intense itching in those areas previously affected by the dermatitis, namely, the antecubitals, wrists, face and neck. Her respiratory symptoms disappeared within 30 minutes after the injection of epinephrine. But some hours later she had a severe exacerbation of the dermatitis involving the antecubitals, wrists and neck, as well as of the face which the patient stated had been clear for some time. The itching was extremely intense, lasting 3 days then gradually lessened until only mild itching remained. Slight wheezing persisted for 2 days. She did well upon specific allergy treatment during 1951 and when seen recently, her skin was entirely clear.

While for obvious reasons we could induce the dermatitis only in two subjects, nevertheless the clear-cut manner in which this was accomplished can be taken as convincing evidence that ragweed pollen was a definite etiologic factor. The sequence of events taking place in the second of these case reports (No. 13) is of some interest, perhaps as an indication of what may transpire in certain patients with atopic dermatitis, especially those with fall exacerbations. It is to be noted that the initial symptoms which followed the injection first were respiratory in character, consisting of sneezing and wheezing. These were present for 24 to 48 hours before the dermatitis began and persisted only 2 to 3 days, whereas the dermatitis remained for a much longer period of time. This sequence suggests the possibility that some ragweed-sensitive patients susceptible to dermatitis first will develop respiratory symptoms, either hay fever or asthma, as a result of exposure to the allergen and

that the dermatitis will develop only secondarily if the reaction is sufficiently marked. This reaction resembles somewhat the constitutional reaction in uncomplicated hay fever patients, in whom only sneezing or mild itching of the skin follows when the reaction is mild, whereas asthma and hives appear when the reaction is more severe.

These observations raise the question as to why ragweed sensitivity should result in uncomplicated hay fever alone in certain individuals, whereas in others it is responsible for asthma usually as a seasonal complication of hay fever or occasionally alone and in still others, atopic dermatitis develops. What is it which determines the type of lesion the patient is to develop? If the shock organs present in the nasal mucosa, bronchial mucosa and skin are interchangeable, one would expect a high incidence of atopic dermatitis in hay fever patients. To determine if this were true, we reviewed the histories of 150 seasonal hay fever patients selected at random from our office files for the incidence of atopic dermatitis. Of the 150, only 4 or 2.7 per cent gave a history of atopic dermatitis (all in infancy). This is indeed a low incidence. Since we know that asthma is a common complication of untreated hay fever, it would seem likely that for most hay fever patients, the bronchial tubes rather than the skin are the more commonly affected shock organ. These observations still fail to throw light on this enigma which is as yet unsolved—namely, what is the factor (called "X" by Hill) which determines when or why one patient gets dermatitis from allergy to ragweed at one time or hay fever and asthma at another or why most patients get urticaria as a part of a constitutional reaction to injections of pollen extract whereas a few get dermatitis from a similar injection.

If the results of these clinical observations and experimental studies with ragweed pollen can be accepted as establishing ragweed pollen as a definite inhalant factor in atopic dermatitis, then this also should be true of other seasonal inhalants notably grasses and molds. While we were primarily concerned with ragweed pollen, it is evident from the results given in Table I that patients with atopic dermatitis have a relatively high incidence of positive skin reactions to timothy pollen, representing our spring grasses, to English plantain and to alternaria, representing our most common atmospheric mold. The incidence is not as high as that of ragweed but as previously mentioned this likewise is true in our patients with uncomplicated hay fever, ragweed being a much more common etiologic agent. We made no attempt to repeat with timothy, plantain, and alternaria the clinical and experimental investigations done with ragweed in order to establish these agents as inhalant factors. In a previous report,[2, 3] we were able to establish alternaria as a specific causative factor both by nasal test and injection. In one other patient in the present series, inhalation of alternaria powder seemed to be followed by some increase in the dermatitis; also in a few instances dermatitis followed the injection of a mixture containing ragweed and alternaria extracts. This made it difficult to tell which one was responsible although the clinical history pointed to ragweed as the more likely cause. Nevertheless, it seems fairly clear that atmospheric molds can be specific causative inhalant factors in atopic dermatitis.

We made no attempt in any of our patients to do nasal tests with either dry timothy or English plantain pollens. The only possible confirmatory evidence of their probable etiologic significance is the fact that 14 of the patients with positive pollen reactions had a clinical history of aggravation of the dermatitis during the early part of the summer coincident with the pollinating season of these plants. This of course is only presumptive evidence of the possible etiologic importance of grass pollens and of plantain. But if it is true of ragweed, it should apply as well to the other pollens. And by the same reasoning, if it is true of those pollens and molds indigent to this area, it likewise should apply to the pollens and molds present in other sections of the country.

Finally, some question has been raised both in the literature on this subject and in personal discussion (Hill, Simon) whether the intracutaneous or scratch tests properly evaluated the sensitivity and whether more information could be obtained by the use of the patch test or scratch-patch using either unaltered pollen or pollen in vaseline or pollen oil. While we do not accept the proposition that they are in any way superior or even as good, to determine this more definitely, we did the following tests on 5 subjects giving definite positive reactions to ragweed by the intracutaneous method: (1) Scratch-patch with dry ragweed pollen, (2) ragweed pollen in hydrophilic petrolatum (25 per cent)—rubbed in hard with applicator and covered with patch, (3) pollen oil (a 1 to 10 mixed ragweed oleoresin in almond oil) patch test, (4) dry ragweed pollen patch test, and (5) dry ragweed pollen moistened with buffered saline patch test.

The reactions in all 5 patients were negative. While the number of patients so tested is admittedly small, it nevertheless suggests that these methods of testing offered no advantage over the intracutaneous method in patients of this type.

COMMENT

From the evidence just presented, we feel justified in concluding that seasonal inhalant allergens, as particularly represented by ragweed pollen, are specific and important inhalant etiologic factors in atopic dermatitis. As previously indicated, the reason why these allergens act in certain predisposed individuals to produce eczematous rather than an urticarial type of eruption is not clear; nor why they induce hay fever, rhinitis, and/or asthma in some and atopic dermatitis in others. This is an unknown, a factor which Hill has chosen to call "X." However, if the results of all our studies to date supplemented by clinical experience with these patients permits the presumption of a hypothesis, it would be as follows: As we all know, when the infant begins his extrauterine existence, the first foreign agents with which he comes into contact are foods and he may become sensitized either to a few or to many. This sensitization need not necessarily be clinical. It may be limited entirely to the skin and never become clinical—hence the great number of nonclinical positives. Or the sensitization may become clinical and be manifested by an eczematous skin eruption (or by colic or vomiting) the skin being an important first line of defense. This clinical sensitization to the foods may be of short duration or it may persist for longer periods. If of short duration, the eruption will disappear because the

child through whatever mechanism, either avoidance or desensitization from continued feeding, overcomes his food allergy. We know this to be true clinically of allergy to milk, egg, orange, etc. Foods now no longer are a factor in the dermatitis, but the positive skin reaction persists, despite the fact that allergy to foods no longer is a factor. What has happened? Well, by this time, the child has been exposed to new allergens, inhalant ones, either perennially as with house dust, or only seasonally as with pollens and molds, and he becomes sensitized by these agents. This new sensitization then manifests itself either as a new outbreak in a previously cleared-up case or by aggravation of an already existing dermatitis which may be seasonal or perennial. With continued exposure, these inhalant allergens then become the most prominent offenders, either completely overshadowing or supplanting food allergens as etiologic agents. If the exposure persists over a long enough period and in sufficiently high concentrations, especially to pollens and molds, there next follows a sensitization of the respiratory mucosa manifested by the appearance of hay fever and/or asthma. This now becomes the major clinical manifestation, either suppressing or supplanting the dermatitis, which either becomes milder or disappears entirely. That this is a distinct possibility is indicated by the frequency with which we obtained a history of alternation between atopic dermatitis or "eczema" in infancy or early childhood supplanted later by hay fever and/or asthma. It is verified too in our own experience in the present series since many more patients gave a history of having had atopic dermatitis first and hay fever and/or asthma later than vice versa.

This sequence of events as to foods and inhalants is generally accepted as being true for bronchial asthma affecting infants and children and if atopic dermatitis is the counterpart in the skin of bronchial asthma, as we believe it is, then the progress of events detailed in the above hypothesis also should apply equally to atopic dermatitis.

CONCLUSION

We have presented evidence both clinical and experimental which we believe proves convincingly that seasonal inhalant allergens as represented by ragweed pollen, are important inhalant factors concerned in the etiology of atopic dermatitis and should deserve proper consideration in the management of these patients.

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EFFECT OF ADRENAL CORTEX IN ALLERGY

I. Effect on Experimental Hypersensitivity

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THE dramatic therapeutic effects of cortisone in allergic diseases has stimulated interest in the role which it plays in immunologic reactions. One might expect that since cortisone is so effective in clinical allergy that it would have a similar effect in experimental hypersensitivity. It was with this thought in mind that we proceeded to determine its influence on (1) precipitin titers, (2) Arthus phenomenon, (3) anaphylaxis, (4) diffuse arteritis, and (5) the Schultz-Dale phenomenon. This paper will also briefly refer to our experience with the effects of Compound F on the induction of active anaphylaxis and the Arthus phenomenon.

The experiments were carried out in actively-sensitized rabbits and guinea pigs.[1] The rabbits were used for the purpose of demonstrating (1) precipitin titers, (2) Arthus phenomenon, (3) diffuse arteritis, and (4) the Schultz-Dale phenomenon. The guinea pigs were used for the purpose of demonstrating gross anaphylaxis and the Schultz-Dale phenomenon.

TECHNIQUE OF SENSITIZATION

Rabbits of both sexes, weighing about 2 kilograms each, were employed. The method of sensitization to horse serum was that recommended by Rich.[2] It consisted of the intravenous injection of 10 ml. of undiluted horse serum per kilogram of body weight, as the sensitizing dose. Subsequent administrations included 1.0 ml. of undiluted horse serum on the seventeenth day, and 10 ml. of horse serum per kilogram again on the nineteenth day. The animals were sacrificed by air embolus on the twenty-sixth day.

The guinea pigs were sensitized with 0.1 ml. of a 1-50 dilution of horse serum intracutaneously. Three weeks later, the shocking dose of 1 ml. of undiluted horse serum was given intravenously.[3]

Precipitins (Table I)

A total of 24 rabbits in this group was studied for precipitin titers. This series was divided into (1) a group of 6 rabbits which received 25 mg. of cortisone subcutaneously daily for 18 days starting with the first day of sensitization, (2) another group of 6 rabbits which received 12.5 mg. of cortisone daily for 1 week prior to and for 18 days following sensitization, (3) a group of 12 rabbits which received horse serum without cortisone. These served as controls. At the end of an 18 day period, blood was obtained from all animals. The serum was separated and the precipitin titer determined by the serum dilution

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technique. This consisted of introducing 0.2 ml. of the antigen (horse serum) diluted 5-5 into tubes to which was added 1.0 ml. of rabbit serum in dilutions of 1-10, 1-100, 1-200, 1-500, 1-1000, and 1-2000. The tubes were incubated for one hour at room temperature and then placed in a refrigerator. They were observed

TABLE I. PRECIPITIN TITERS OF RABBITS TREATED WITH CORTISONE BEFORE AND DURING SENSITIZATION, AND OF UNTREATED CONTROLS

PRECIPITIN TITER	CORTISONE		CONTROL
	DURING	PRIOR AND DURING	
1-2000	1	0	1
1-1000	1	0	2
1-500	2	1	3
1-200	1	3	2
1-100	1	1	3
1-10	0	1	1
Total	6	6	12

for the formation of a precipitate at the end of 24 and 48 hours. The tube containing the highest dilution of rabbit serum showing the precipitate was taken as the final titer reading. The serum precipitin titers of the first group of 6 rabbits receiving 25 mg. of cortisone daily for 18 days, showed the following: 1 animal, a titer of 1-2000, 1 of 1-1000, 2 of 1-500, 1 of 1-200, 1 of 1-100, 0 to 1-10. The serum precipitin titers of the second group of 6 rabbits, which received 12.5 mg. of cortisone for 1 week prior to, and for 18 days following sensitization, showed the following: 1, a titer of 1-500, 3 of 1-200, 1 of 1-100, and 1 of 1-10. The serum precipitin titers of the third group of 12 control animals showed the following: 1 titer of 1-2000, 2 of 1-1000, 3 of 1-500, 2 of 1-200, 3 of 1-100, and 1 of 1-10. It was realized that the quantitative antibody determination method is more accurate than the dilution method, but this method is not applicable to a mixed antigen such as horse serum. The variations in precipitin titer (Table I) are not significant but may well be due to chance. It may therefore be concluded that the precipitin titer of rabbits treated with cortisone during or prior to and during sensitization was no different from that of the controls.

ARTHUS PHENOMENON

A total of 20 rabbits were sensitized with horse serum. One group consisted of 10 rabbits which received 25 mg. of cortisone subcutaneously daily starting with the day of sensitization and continuing daily for 18 days. The Arthus phenomenon was performed on the twelfth day after the initial injection of horse serum. It was produced by injecting 1 ml. of horse serum partly intracutaneously and partly subcutaneously. Of these 10 rabbits, 2 showed a negative and 8 animals showed a positive Arthus reaction. In the control group of 10 rabbits the Arthus phenomenon was negative in 3 and positive in 7 animals. The severity of positive reactions was analogous in the test and control groups. It may be seen therefore that there was no appreciable difference as to the incidence and severity of the Arthus phenomenon between the two groups—those that received cortisone, and the controls which did not (Fig. 1).

This experiment was repeated using Compound F instead of cortisone. Compound F (17-Hydroxycorticosterone) is secreted predominantly by the adrenal cortex. It has been indicated recently that when injected locally into affected joints, compound F has an increased therapeutic effect as compared with cortisone; it has been stated that "milligram for milligram" it is more potent than cortisone.[4] A group of 10 sensitized rabbits received 25 mg. of Compound F subcutaneously daily starting with the day of sensitization and continuing daily for 18 days. Of these 10 rabbits, 2 showed a negative Arthus phenomenon, the other 8 animals showed a positive local reaction. Again there was no appreciable difference in the incidence and severity of the Arthus phenomenon between the controls, cortisone-treated animals and those that received Compound F. The Arthus phenomenon when positive was characterized by redness, swelling, and necrosis of the local skin site. Microscopic sections of the lesions showed necrosis of the cells of the uppermost epidermis. The underlying dermis was packed with a cellular exudate consisting of lymphocytes, polymorphonuclear leukocytes, eosinophils, and plasma cells. The collagen fibers showed fibrinoid degeneration and even the underlying tissue showed leukocytic infiltration around the bundles.

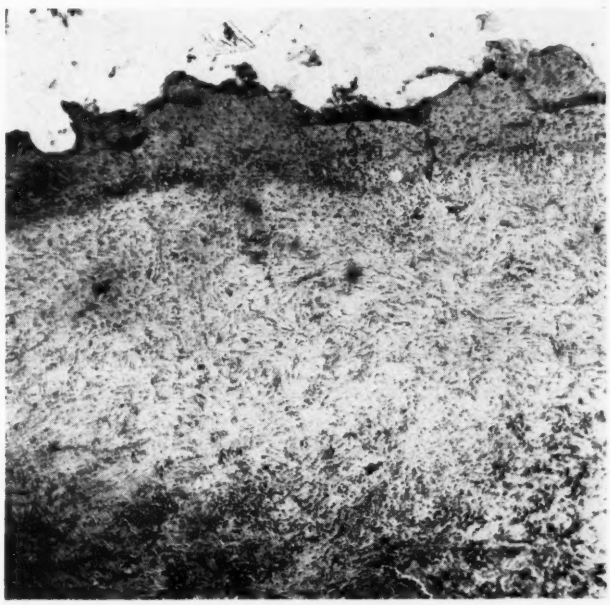

Fig. 1.—Positive Arthus phenemenon—microscopic section. Animal treated with cortisone. No inhibition of reaction.

ANAPHYLAXIS

For the study of anaphylaxis 28 guinea pigs were used. Of these 10 animals constituted the controls. All of these animals died in anaphylaxis when properly shocked. A second group of 6 guinea pigs received 10 mg. of cortisone daily for 7 days prior to sensitization. Twenty-one days later a shocking dose of 1 ml. of undiluted horse serum was given intravenously. All of these animals also died in anaphylactic shock. A third group of 12 guinea pigs was given 15 mg. of

cortisone daily for 21 days beginning with the day of administration of the sensitizing dose and extending through the entire period of sensitization. The shocking dose of 1 ml. of undiluted horse serum was injected intravenously on the twenty-first day. All of these animals died of anaphylactic shock. All 28 guinea pigs therefore died in shock. Cortisone given before the sensitizing dose and during the entire period of sensitization failed to protect the guinea pigs against anaphylactic shock. It is fair to point out that the method of sensitization and shocking was such as to produce 100 per cent fatal results in the control animals. Hence only a very powerful modifying agent might be expected to affect the results.

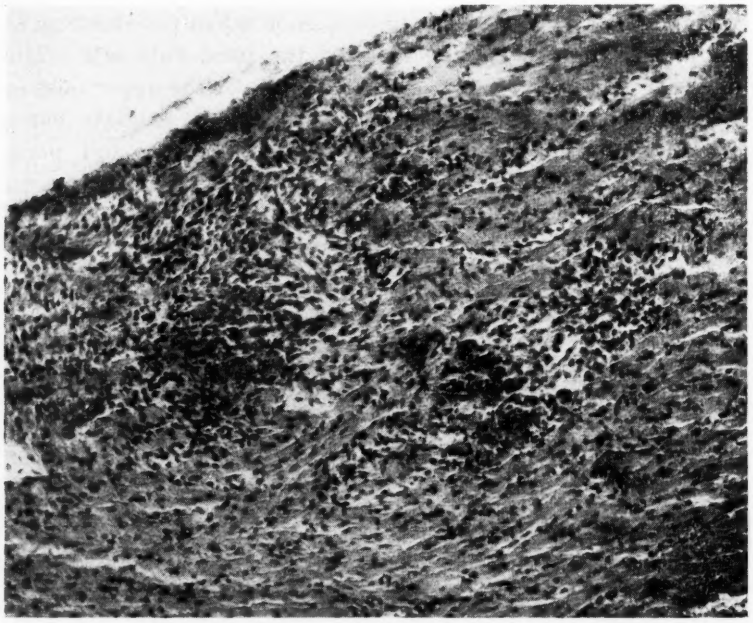

Fig. 2.—Diffuse vascular changes in untreated animals.

This experiment was repeated using compound F instead of cortisone. A group of 10 guinea pigs was given 25 mg. of compound F daily for 21 days beginning with the day of the administration of the sensitizing dose and extending through the entire period of sensitization. The shocking dose of 1 ml. of undiluted horse serum was injected on the 21st day. Like cortisone, compound F failed to protect the guinea pigs against anaphylactic shock.

DIFFUSE ARTERITIS (VASCULAR ALLERGY, COLLAGEN CHANGES)

A total of 14 rabbits were sensitized by the Rich technique for the experimental production of vascular lesions. The first group of 10 rabbits received 25 mg. of cortisone subcutaneously daily for 26 days beginning with the first day of sensitization. The second group consisted of 4 animals which were used as controls. Sections of the heart, lungs, spleen, pancreas, adrenals, and kidneys were examined after fixation in formalin and stained with hemotoxylin and

eosin. Pathologic study of microscopic sections of the control group revealed the following: The lesions included perivascular infiltration of blood vessels with lymphocytes, plasma cells, and eosinophils. The myocardium showed infiltration with plasma cells and lymphocytes with myocardial degenerations. The lesions seen on microscopic study of the tissues of these animals were graded according to the following criteria: none, no lesions seen; very slight (1+), one or two small venules showing perivascular infiltration usually only in the lungs; slight (2+), when only a minor infiltration of round cells was seen in the myocardium plus one or two venules showing perivascular round cell infiltration of the lungs alone; moderate (3+), when two or three lesions of round cell infiltrations were observed in one section or only two lesions seen in two or three sections; marked (4+), lesions showing extensive infiltration of round cells in the myocardium and extensive perivascular infiltration in the viscera.

Five of the 10 rabbits treated with cortisone showed a very slight (1+) involvement and the remaining 5 animals showed a slight (2+) involvement. Pathologic examination of the control group of 4 animals showed extensive (4+) lesions in all animals. The lesions were characteristic of periarteritis nodosa and rheumatic carditis as described by Rich and Gregory. Cortisone definitely decreased the formation of vascular lesions (Figs. 2 and 3).

SCHULTZ-DALE REACTION

A total of 6 rabbits was studied in this experiment using 3 sensitized rabbits as controls and 3 animals treated with 25 mg. of cortisone daily for 18 days. Muscle strips from the ileum were taken immediately after death and were suspended in Tyrode solution. To the bath was added 0.1 ml. to 0.4 ml. of undiluted horse serum. The 3 animals treated with cortisone revealed negative reactions. In the control group the intestinal strip of one animal showed a positive Schultz-Dale reaction and the remaining 2 failed to react. One would hesitate, however, to draw any conclusions from this experiment in view of the fact that this test is especially unsatisfactory when dealing with the rabbit's isolated ileum strip.

A total of 10 sensitized guinea pigs was also studied. Muscle strips from the ileum were taken immediately after death and were suspended in Tyrode's solution. Three animals out of this group served as controls. In tests on the second group of 7 animals, 25 mg. of cortisone was added to the Tyrode solution. In both the control and test group, a positive Schultz-Dale reaction was obtained with no variation of muscle contractibility. Cortisone when added locally to the bath did not alter the reaction of the sensitized muscle strip.

DISCUSSION

A discussion of the role of the adrenal cortex in experimental allergy includes the following:

1. The effect of Coristone on certain immunologic phases of experimental hypersensitivity in the intact animal.

2. The effect of cortisone on experimental hypersensitivity in the adrenalectomized animal.

3. The effect of adrenalectomy alone on these phenomena.
4. The relation of our findings to the effect of cortisone in clinical allergy.

It would appear from our present work that cortisone in the intact animal if administered during, or prior to and during, sensitization does not affect the precipitin titer. Anaphylaxis and the Arthus phenomenon are also unaffected. However, cortisone does seem to inhibit the development of experimental collagen changes such as diffuse arteritis. As regards anaphylaxis, other workers, notably

Fig. 3.—Inhibition of diffuse vascular changes in rabbit treated with cortisone.

Malkiel,[5] Leger, Leith and Rose,[6] and Friedlander[7] have been unable to prevent anaphylactic shock by the administration of ACTH or cortisone in the intact animal, regardless of whether these substances are administered before or during the period of sensitization. Furthermore, Berthrong, Rich and Griffith[8] inhibited the production of diffuse arteritis by the administration of cortisone or ACTH, results consistent with our findings. On the other hand, other workers, particularly Germuth and Ottinger[9] using a slightly different sensitization technique demonstrate a suppression of antibody titer with ACTH and cortisone. They find that antibody production of ACTH-treated animals was 50 per cent less than the control series. With cortisone, the suppression was even greater than 50 per cent. In their hands, treatment of animals with steroids inhibited both the production of precipitins and of the Arthus phenomenon. Their work however does not include anaphylaxis and diffuse arteritis. Quantitative antibody titers resulting from sensitization with

pneumococcus vaccine were lower in rabbits receiving ACTH or cortisone. The titers also fell when cortisone or ACTH was started 14 days after sensitization.[10] Still other workers obtained even different results. For example, White and Dougherty[11] indicate that the administration of these hormones in the intact animal causes a rise in antibody titer. They explain this as being due presumably to a lysis of lymphocytes. These changes have been contradicted by many. Thus, Fischel, LeMay, and Kabat[12] using the quantitative technique in intact rabbits could not confirm their results. Furthermore, Eisen and associates[13] state that these hormones do not produce a prolonged effect on the formation or release of antibodies. Similar conclusions were reached by DeVries[14] who discovered that ACTH although producing lymphocytopenia does not cause a release of antibodies into circulation. Furthermore, no rise in gamma globulin has been found to occur after treatment with ACTH in man.[15-19] Whether the lymphopenia which follows the administration of cortisone is the result of lympholysis or concentration of lymphocytes in the tissues[20] is not definitely known, but the evidence would seem to favor the latter view; and it would appear that while the lymphocyte may be considered as a source of antibody, there is serious doubt as to whether lymphocytic disintegration may yield a material increase in antibody titers. It is possible that the divergence in the findings enumerated above may be due, among other reasons to a difference in technique or to a difference in the time of the determination of precipitin titers. In relation to the latter point, it should be said that Halpern and associates[21] found that in the first 48 hours following the injection of antigen, the level of antibodies in the sera of animals treated with cortisone was significantly higher than that of the controls. After the third day, the production of antibodies of the treated animals was found to be much lower than that of the controls.

What is the effect of cortisone on these various phenomena of sensitization when cortisone is administered to adrenalectomized animals? White and Dougherty indicate that no change in antibody titer results when cortisone is administered to adrenalectomized animals. Eisen and associates[13] working with adrenalectomized rats found the same antibody titer after adrenal cortical extract was administered. They also found no appreciable change on antibody production after administration of adrenal cortical extract. On the other hand, the administration of adrenal cortical extract in adrenalectomized animals according to Wolfram and Zwemer[22] results in greater resistance to anaphylactic shock.

So much then for the results obtained in experimental hypersensitivity following the administration of cortisone to the intact and to the adrenalectomized animal. As background for this information, we have previously demonstrated experimentally[23] that the removal of the adrenals enhances the precipitin titer, anaphylaxis, the Arthus phenomenon, and experimentally produced diffuse arteritis. The question arises as to why adrenalectomy should have such an effect. The answer is not clear. The adrenal cortex is well known to control the number of circulating lymphocytes. Our observations as well as those of others seem to indicate that there is an inverse proportion between

adrenal cortical activity and lymphoid mass.[24] As pointed out by Gordon and Katsh[25] the adrenal cortex has a profound influence upon the phagocytic activity of the reticulo-endothelial system resulting in hypertrophy of lymphoid tissue. This plays an important role in antibody formation and may account for the presence of increased antibodies. One may speculate further into other mechanisms which enhance these various immunologic processes. Adrenal cortical extract depresses fibroblastic activity. The fibroblast is thought by many observers to be the basic cell of the reticuloendothelial system. It is possible that removal of the adrenals may enhance mesenchymal or fibroblastic proliferation which could account for a rise in antibody titer.

In man, the administration of cortisone produces immediate relief from severe intractable allergic diseases such as asthma, urticaria, hay fever, atopic dermatitis, and contact dermatitis. Furthermore, even in the delayed inflammatory type of allergic diseases such as vascular allergy—periarteritis nodosa and possibly lupus erythematosus, cortisone will benefit these conditions if administered during the period of early inflammation when the changes are still reversible. How this is brought about is not exactly clear. Apparently the dramatic clinical effect of cortisone is not due to reduced antibody formation. However it is possible that it may interfere with antigen-antibody union or affect the cell in such a way that it does not liberate the histamine-like substance following the antigen-antibody reaction, or through some other, as yet undisclosed, chemical or enzymatic mechanism.

It is generally thought that the acute edematous clinical allergic reactions, namely, asthma and urticaria, are brought about by a mechanism similar to that of acute anaphylactic shock. In other words, the localized edema is produced by a histamine-like substance liberated as the result of antigen-antibody union. If this is so, then one might logically expect that cortisone would affect anaphylaxis and related experimental phenomena, in the same way as it affects the analogous immediate allergic reaction of asthma. However, our results do not substantiate this expectation for we find that the steroids have no significant influence on the precipitin titer, and no inhibitory influence on the Arthus phenomenon or anaphylaxis.

SUMMARY AND CONCLUSIONS

Cortisone does not affect the precipitin titer if administered during or prior to and during sensitization. The Arthus phenomenon, anaphylactic shock and the Schultz-Dale reaction in the isolated ileum strip performed in the manner described remain unaffected. Cortisone tends to inhibit experimental diffuse vascular reactions.

Anaphylactic shock and the Arthus phenomenon are unaffected by the administration of Compound F.

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HEMATOLOGIC MANIFESTATIONS OF AN ALLERGIC NATURE

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ALTHOUGH it is common knowledge that the plasma proteins of blood are antigenic, it is less frequently brought to mind that the formed elements of the blood may also sensitize (or be sensitized against). The demonstration by Landsteiner of the natural isoagglutinins that determine human blood types was followed throughout the first two decades of the present century by a host of experiments, by different investigators, which established beyond a doubt that mammalian erythrocytes, white cells and platelets all had this property. Bedson[1] demonstrated that this reaction was cytologically specific, e.g., an antiplatelet guinea pig serum would cause thrombocytopenia but not anemia or leukopenia, while an antileukocyte serum would cause only leukopenia, and an antired cell serum would cause only anemia.

By definition heteroimmunization is the immunization of a subject by cells of a different species, isoimmunization by cells of his own species but from a different subject, and autoimmunization is the sensitization of an individual by his own blood cells. One of the peculiar things about blood cells is that they appear capable under certain circumstances of becoming autoantigenic. This is confusing because it seems to be a violation of the principle of species specificity. It is easy to understand how blood cells of a different type can sensitize a recipient with resulting severe reactions attending subsequent exposure, for this follows the basic pattern of all immune reactions. It is more difficult to account for the appearance *de novo* of auto-immune bodies that destroy a patient's own blood cells, as occurs in many acquired hemolytic anemias. Nevertheless, it happens, and we are gradually beginning to understand some of the mechanisms involved.

To start with the simplest and best understood field, let us consider the natural blood groups. Red blood cells contain agglutinogens A, B, both, or neither. (There is now good evidence that group O, originally considered to be without agglutinogens, has its own antigen, which may be a sub group variant of A.[2]) These cells are respectively agglutinated by the natural isoagglutinins alpha and beta, present in the plasma proteins. At low temperatures it is possible to demonstrate isohemolysins of corresponding types, as well.[3] The plasma of any individual contains the agglutinin only for the types of cell not present, otherwise autoagglutination would occur. When incompatible blood is transfused isoagglutination and hemolysis result, a danger that, by now, is well recognized.

In addition to the major isoagglutinogens, red cells also contain other antigenic factors. At the present time there are 9 recognized blood group systems, named empirically, or as is now the vogue, after the family or hospital

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in which they were first studied. They contain at least 25 different antigenic factors, most of which are of such low antigenicity, or so widespread in the population, that they are of clinical importance only in rare instances. These systems with their empiric designations are the A-B-O, Rh-Hr, M-N-S-s,[4] P-p, Kell-Cellano (K-k),[5] Duffy (Fy^a-Fy^b),[6] Lewis (Le^a-Le^b-ABO secretor),[7] Kidd (Jk^a-Jk^b),[8] and Lutheran (Lu^a-Lu^b).[9] In addition many miscellaneous factors have been demonstrated in different families, and designated by their names, e.g., Levay, Jobbins, Jay, Miltenberger, etc., which have not yet been studied sufficiently to be established as universal systems. With the exception of the Rh-Hr group, the chief importance of these systems at present is in identifying blood specimens and disproving paternity.

By now it is a familiar story how Landsteiner and Wiener[10] discovered that antirhesus monkey red cell rabbit serum agglutinated 85 per cent of human red blood cells, and called the responsible factor the Rh agglutinogen. Wiener and Peters[11] indicated it was responsible for some previously inexplicable transfusion reactions, and Levine[12] observed that such reactions were very common in pregnant women who received post partum transfusions with blood supplied by their husbands. He surmised that they must have been sensitized by their offspring in utero, and this led to the discovery of the relationship between Rh isosensitization and the disease of the newborn, erythroblastosis fetalis. This disease is now known to be due to the sensitization of a mother by her fetus. This occurs usually in an Rh-negative woman, into whose blood stream the red cells of an Rh-positive fetus find their way through the placenta. She may react to this stimulus by forming two kinds of antibodies: so-called "bivalent" agglutinins that bind the Rh-positive red cells together in clumps in vitro, and "univalent" antibodies which are much smaller and coat the red cells so that they cannot be agglutinated in vitro, but may subsequently be destroyed in the body. It is the latter type of antibody that is believed to be chiefly transmitted to the fetus from the maternal side of the placenta[13] to cause the extensive damage to the blood, liver, and brain that characterizes erythroblastosis. Modern methods of therapy of this disease are designed to remove such coated cells from the circulation of the newborn, and replace them with Rh-negative cells. This is called exchange transfusion.

The detection of such antibodies coating the cells is facilitated by the use of an immunologic method, based on the fact that these antibodies are globulins. If rabbits are immunized with Type O plasma, or human gamma globulin, the resulting rabbit serum will agglutinate globulin-coated cells. This is the Coombs test.[14, 15] It is not limited to Rh sensitization but will also be positive in acquired hemolytic anemias due to other autoantibodies[16] and will agglutinate blood coated by cold hemagglutinins. In the latter case the test becomes negative when conducted at body temperature.

At the present time there are known to be three Rh agglutinogens designated, Rh_0, rh′ and rh″ by Wiener[17] and D, C and E by Fisher.[18] There is also a sub-variant of rh′, called rh^w (C^w).[19] Individuals who lack any or all of these three factors have, instead, genetically related agglutinogens designated Hr_0, hr′ and hr″ (d, c and e).[20] These are much less strongly antigenic

than the Rh groups, but may occasionally give rise to sensitization and hemolytic disease. For a lucid and detailed review of the entire subject of the Rh-Hr blood group system the reader is advised to consult the monograph by Potter.[21]

For years idiopathic acquired hemolytic anemias were observed to occur, but it was not until Dameshek[22] republicized the 25-year-old observations of the French and Italian investigators that they were generally recognized to be due to autoimmune reactions. The advent of the Coombs' test made it possible to demonstrate the presence of an antibody coating the cells in many such cases.[23]

The spleen has been shown to be a major site of antibody formation in man.[24] It was also demonstrated by Wagley and associates[25] that incubating blood with emulsions of spleens removed from patients with acquired hemolytic anemia, rendered the blood specimens Coombs' positive. These facts help to explain the beneficial results of splenectomy in some such patients, while the failure of the same operation in others may be attributed to a greater degree of antibody formation in these cases, by tissues other than the spleen. The antibody coating the cells is thought to make them more adherent to each other, forming rouleaux or clumps that are agglutinated in the spleen or end capillaries, producing stasis and resulting hemolysis.[26]

The greatest mystery is how the antibodies are formed in the first place. Many bacteria and viruses have the property of agglutinating red cells in vitro,[27, 28, 29] and the association of hemolytic anemias with clinical infections is well established.[30] The infecting agents appear to coat the red cells (probably due to similarities of prosthetic groups on their molecules of specific antigenic substance and molecules on the surface of the red cell) which are then agglutinated by specific antibodies formed against the bacteria.[31] It has been shown, for example, that some of the chemical constituents believed to be responsible for the antigenic properties of the pneumococcus (e.g., d-glucosamine) are also present in the red cell envelope.[22] It appears possible that antibodies formed following acute infections with suitable organisms may hemolyze red cells, liberating more antigen in the process and initiating a self-perpetuating state of autoimmunization. This may spontaneously subside, or it may become increasingly severe and ultimately fatal unless it is interrupted by splenectomy.

Cold agglutinins have already been mentioned. They arise after various infections, particularly virus pneumonia. Being essentially an in vitro phenomenon, inactive at body temperature, they do not usually cause hemolysis in the body. A few cases have been reported of hemolytic anemia, associated with enormously high titers of cold agglutinins.[33, 34] In some of these cases it was possible to initiate clinically detectable hemolysis by chilling an extremity (Rosenbach test).[35]

A rare type of autohemolysin activated by chilling was described by Donath and Landsteiner, and shown to be responsible for cases of paroxysmal hemoglobinuria. The disease occurs mostly in patients with refractory syph-

ilis. Normal blood cells, incubated in the icebox with complement free serum of these patients, will hemolyze upon being warmed to 37° C., if complement is added.

PURPURA AND THROMBOCYTOPENIA

Anaphylactoid purpura is an acute, generalized purpuric state due to increased capillary permeability. There is no demonstrable defect in the blood clotting mechanism or the formed elements of the blood, but the Rumpel-Leede test is positive, and there is generalized purpura and frequently, epistaxis, menorrhagia and gastrointestinal bleeding. Joint pains are usually prominent and gastrointestinal symptoms of pain and vomiting may occur. The disease usually comes on suddenly and disappears spontaneously after a varying period of time. It has been attributed to many different kinds of sensitivity,[36] but in my experience it is exceptional to be able to incriminate a specific allergen in these cases, and many of these subjects give no history of other allergies. We have been struck by the frequency with which this disease occurs in individuals with a previous history of rheumatic attacks and by the presence in some of an elevated antistreptolysin titer. It is unusual to find rheumatic heart disease in these patients, however. While I would not go so far as to say that such cases are manifestations of rheumatic fever, I do believe, that like that disease, the majority of cases of anaphylactoid purpura represent hyperergic vascular responses to infection, often with hemolytic streptococci.[27] This puts anaphylactoid purpura in the same category as rheumatic fever, acute nephritis, and possibly periarteritis nodosa, all of which conditions, incidentally, may have purpura as one of their presenting symptoms.

Thrombocytopenic purpura may also arise as the result of sensitivity reactions. Toxic thrombocytopenias occurring in some individuals who take certain drugs (many of whom have previously taken them for some time without ill effect), while other individuals may take the same drugs with impunity, are undoubtedly due to drug sensitization.[38] In these cases the removal of the offending drug will usually suffice to stop the purpura. There is also some evidence to suggest that idiopathic thrombocytopenic purpura, with no demonstrable drug or toxic factor may also be the result of immune mechanisms, similar to those previously discussed with reference to hemolytic anemias. Harrington[38a] has produced thrombocytopenia in normal subjects by transfusing them with blood or plasma from patients with idiopathic thrombocytopenia, which is evidence that their plasma contains an antiplatelet factor, humoral or immunologic in nature. Evans[39] pointed out the occasional coexistence of idiopathic thrombocytopenic purpuras and acquired hemolytic anemias with positive Coombs tests, and assumed that the thrombocytopenia in these states is due to autoagglutination and destruction of platelets. (We have not been impressed with the frequency of coexistence of positive Coombs' tests in our own cases of thrombocytopenia.) He demonstrated in vitro agglutination of platelets by the plasma of some of his patients. This is, however, very difficult to do with present methods. Unfortunately, up till now no one has been able to devise a Coombs' test for platelets that will demonstrate their being coated with anti-

body. This is perhaps due to the fact that as soon as they are coated, they are agglutinated and destroyed. According to this theory of the etiology of thrombocytopenia the beneficial effect of splenectomy in such cases may be attributed to the removal of a primary site of antibody formation.

LEUKOPENIAS AND APLASTIC ANEMIA

In addition to thrombocytopenia, neutropenia and agranulocytosis are also well-known complications of therapy with certain drugs. That this is probably a true hypersensitization was shown by Dameshek[40] who found that the agents in question could give positive skin tests in sensitized patients, if they were first incubated with human serum. (To our knowledge this has not yet been confirmed.) Since the drugs themselves are often not proteins, they apparently combine with one of the plasma proteins to form a new substance capable of reacting as a "foreign protein" in the host. The ability to form this combination or form antibodies against it is probably the basis for the differences in susceptibility of various individuals to this type of reaction. It appears that the white cells are inhibited in their formation by such antibodies, and the removal of the toxic drug is usually followed by a gradual reappearance of neutrophil precursors in the bone marrow.

Aplastic anemias also occur due to the toxic effects of drugs. Some of these anemias are due to the direct action of the drug on the marrow (e.g., nitrogen mustard), and when the offending agent is removed recovery ensues fairly quickly. In other cases, however, the hypoplastic state persists long after the etiologic factor has been eliminated. Such cases are probably due to a hypergic reaction involving the red cell precursors, and often all the formed elements of the blood. Such reactions sometimes occur in patients who have had frequent blood transfusions.[41] The reasons for this are not clear. It may be a general reaction to type specific antibodies or it may be a foreign protein reaction.

Little is known about the role of specific types of leukocytes in the production of immune reactions. Lymphocytes are generally believed to play a role in antibody formation, and eosinophils are usually present in the tissue involved in an allergic reaction, and are frequently increased in the peripheral blood of allergic subjects. Eosinophilia is marked in parasitic infestations, particularly where the parasites are implanted directly into the body tissues as in trichinosis, hookworm, and schistosomiasis. It is also frequently seen accompanying the administration of antibiotics, and in serum sickness. In periarteritis nodosa and rheumatic fever, eosinophilia frequently occurs, and also in patients with pernicious anemia who are receiving liver injections (many of whom develop clinical sensitivity to liver extracts). Finally, in heavy metal therapy eosinophilia is regularly encountered. The height of eosinophilia is no index to the incidence or severity of reactions to gold salts,[42] but nearly all patients who develop such complications show some eosinophilia, so while it is not a contraindication to continued therapy it should, at least, be regarded as a warning. All this evidence indicates that eosinophils have something to do with immune reactions, but the nature of their function in

this regard is obscure. The relation between eosinophil levels and adrenal cortical activity suggests that this gland may play some role in these blood changes.

This leads us finally to the problem of therapy. I have already indicated that it is possible to correct the situation by removing offending antigens in the form of toxic drugs or foods, in some cases, or by exchange transfusion in cases of Rh isosensitization. In other cases such as idiopathic thrombocytopenia and acquired hemolytic anemia, splenectomy often checks the disease by removing a primary site of blood destruction (antigen liberation) and antibody formation.

Antihistamines have not been of much use in hematologic allergies, the reason being that they neither prevent sensitization nor the union of antigen and antibody, but merely neutralize the effects of histamine liberated in the tissues which are the site of the reaction. Thus, while they might ameliorate or mask the symptoms of a transfusion reaction they would not prevent hemolysis from taking place.

The most interesting recent therapeutic agents introduced are ACTH and cortisone. These drugs have been shown repeatedly to check acquired hemolytic anemias,[43] thrombocytopenia,[44] and anaphylactoid purpura.[45] With their aid we have been able to induce new blood formation in hypoplastic and agranulocytic marrows. Unfortunately for the patient, the effects are usually withdrawn with the drugs; exasperating for the clinician, we have so far been unable to produce consistent results. It is impossible to predict on the basis of our present knowledge which cases of hemolytic anemia or purpura will respond to cortisone. It seems most likely that if we consider these diseases to be immune responses, then their response to steroid hormones depends on the property of these drugs to influence such reactions.[46, 47, 48] If this is so, it appears likely that the inconsistent results are due to individual variations in the severity of the immune reaction in relation to the doses of drug employed. If more potent or more specific hormones should become available in the future, more consistent results might be anticipated.

SUMMARY

The immunologic nature of certain hematologic disorders has been reviewed and discussed. These include transfusion reactions, Rh isosensitization, acquired hemolytic anemias, purpuras (anaphylactoid and thrombocytopenic), agranulocytosis, and aplastic anemia. Possible mechanisms of pathogenesis and indications for treatment are briefly considered.

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Erratum

In the article by Carl E. Arbesman et al. (page 293, July issue), the lot number of the ACTH was incorrectly stated. The number should read J21812.

Editorial

STANDARDIZATION OF ALLERGENIC EXTRACTS

In a recent letter to the editor, an allergist asks what can be done to standardize the materials used in the diagnosis and treatment of allergic diseases. This is a problem to which the JOURNAL cannot offer a solution, but one which physicians devoting their time to allergy would do well to ponder and to which the national allergy societies might be able to work out a solution. For essentially all important medications used in other fields of medicine standards of identity, purity and potency have been established by the Pharmacopeia and the United States Public Health Service, so that the purchaser, whether physician or patient, is assured of what he is getting, regardless of the source. On the other hand, no standards have been established for such widely used allergenic extracts as low ragweed and dog epithelium and the allergist can judge the value of materials he is using only by previous knowledge of the maker. In the absence of standards, there is no real assurance even that batches of the same allergen prepared by the same manufacturer in different years will be identical. The principal reason for this situation is the failure of allergists to agree among themselves on suitable specifications.

The prevailing attitude of allergists, both those who prepare their own extracts and those who obtain them from other sources, seems to be that the materials they use are producing satisfactory results and that a change would be inconvenient and unwarranted. To patients and physicians in other fields of medicine this complacency seems less justified. The patient under treatment by one allergist, who moves to a new locality and consults a different physician is apt to find that he is essentially starting treatment again at the beginning. Even the repetition of skin tests using another make of extracts often leads to divergent results which confuse the patient and lessen his confidence in the whole practice of allergy. General practitioners and specialists in other fields are apt to regard allergists as a peculiar cult injecting patients with mysterious brews of house dust, dog hair, and other substances reminiscent of the primitive witch doctor. The enthusiasm with which general practitioners have welcomed each new type of nonspecific treatment for allergic disease, from histaminase to cortisone, is not surprising. Efforts by allergists to secure recognition of their field as an important medical specialty with a sound scientific basis, are no doubt hampered by the fact that a large proportion of the materials they use are of uncertain composition and potency.

The widespread practice of preparing allergenic extracts in the office or clinic resulted from obvious necessity in the pioneering days. Regardless of

the number of standard extracts available, the need for improvisation to cover unusual contacts of occasional patients will still remain. The extent to which small scale preparation of widely used extracts such as those of low ragweed pollen or dog epithelium is now justified is an open question, but certainly there is no justification for the use in hundreds of laboratories of such varied methods of preparation and measuring potency that scarcely any two extracts are interchangeable. Even those who prepare their own allergens would regard with suspicion a cardiologist who used only digitalis grown in his own garden or a specialist in diabetes who manufactured insulin for his own patients.

The Public Health Service has established standards for the collection, purity and preservation of dry pollens for use in making extracts and also for the bacteriologic purity of the extracts. The problem of formulating acceptable uniform methods for preparing extracting fluid, carrying out the extraction, and preserving the extract has not been solved. Nor have the problems presented by allergenic materials inherently more variable than pollens, such as house dust and animal danders.

No unanimity of opinion has yet been reached as to the measures of potency of allergens, some laboratories expressing potency in terms of dilutions of the concentrated extracts prepared by their particular methods, others in terms of the weight of original material per volume of extract, still others by the total nitrogen content or the protein nitrogen content. If a pure and properly preserved pollen is extracted by a standard method all of these measures of potency may be expected to yield reasonably parallel results, but if the extracting fluid, the proportions of pollen to fluid, or the conditions of extraction are varied even the approximate relationship is lost. In the preparation of extracts of animal danders, the original materials are necessarily variable and impure, and it is generally impractical to mechanically separate the active allergen from a large amount of insoluble hair. In such cases, the weight of material extracted is of no value as a measure of potency, the determination of total nitrogen includes non-allergenic impurities such as urea, and the protein nitrogen offers the most practical means.

As has been pointed out by proponents of the protein nitrogen standardization, the active material of all the common allergens that have been adequately studied is included in the protein nitrogen determined by phospho-tungstic acid precipitation. On the other hand, most allergen extracts as usually prepared are complex mixtures of several different proteins, only one or two of which may be allergenic for a particular patient. However, since another patient may react to other proteins in the mixture, the protein nitrogen appears to offer the best chemical standard yet developed. Biologic methods of standardization have been proposed, but none so far has gained acceptance as a practical routine measure. On theoretical grounds it appears unlikely that any simple biologic standardization would adequately solve the problem presented by a natural mixture of proteins, to some of which one patient is sensitive while another reacts to others.

Without attempting to settle the question of what standards should be established, it may be noted that the Veterans Administration has found it

advantageous to use in all of its institutions, allergens prepared in one central laboratory. The Armed Forces have adopted uniform standards of preparation and potency for allergens used in their clinics and hospitals. With these specifications, materials supplied by various manufacturers have proved essentially interchangeable. In both instances, it has been felt that the uniformity of materials used was helpful to raise the level of allergic diagnosis and treatment. Also the advantages in continuing treatment of patients transferred from one station to another are obvious.

Allergists in civilian practice would do well to consider whether the general standard of allergic diagnosis and treatment could not be improved if a specified dose of dog epithelium represented exactly the same type and amount of material whether given in Boston, Chicago or Los Angeles. If a large proportion of allergists feel that such uniformity is desirable, it should be possible to reach an agreement as to what specifications are to be adopted.

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